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(54) Title: IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF OBESITY

(I)

(57) Abstract: This invention relates to substituted imidazole derivatives of formula I, which have been found to suppress appetite and induce weight loss. The invention also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders.

WO 03/040107 A1

IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF OBESITY

This application claims benefit of U.S. Provisional Application Serial No. 60/324,473, filed September 24, 2001, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to the field of pharmaceuticals, in particular to the field of obesity treatment. More specifically, it relates to certain imidazole compounds which are useful in the treatment of obesity and obesity-related disorders, and as weight-loss and weight-control agents.

BACKGROUND OF THE INVENTION

Obesity, which is defined as an excess of body fat relative to lean body mass, is a well-established risk factor for a number of potentially life-threatening diseases such as atherosclerosis, hypertension, diabetes, stroke, pulmonary embolism, sleep apnea, and cancer. Furthermore, it complicates numerous chronic conditions such as respiratory diseases, osteoarthritis, osteoporosis, gall bladder disease, and dyslipidemias. The enormity of this problem is best reflected in the fact that death rates escalate with increasing body weight. More than 50% of all-cause mortality is attributable to obesity-related conditions once the body mass index (BMI) exceeds 30 kg/m^2, as seen in 35 million Americans (Lee, JAMA 268:2045-2049, 1992). By contributing to greater than 300,000 deaths per year, obesity ranks second only to tobacco smoking as the most common cause of potentially preventable death (McGinnis, JAMA 270:2207-2212, 1993). Accompanying the devastating medical consequences of this problem is the severe financial burden placed on the health care system in the United States. It is estimated that 30-50% of the middle-age population may be considered as obese (Kuczmarski et al., JAMA 272:205-211, 1994). The economic impact of obesity and its associated illnesses from medical expenses and loss of income are reported to be in excess of $68 billion/a year (Colditz, Am. J. Clin. Nutr. 55:503S-507S, 1992). This figure does not include the greater than $30 billion per year spent on weight loss foods, products, and programs (Wolf, Pharmacoeconomics. 5:34-37, 1994).

The accumulation or maintenance of body fat bears a direct relationship to caloric intake. Comprehensive treatment programs, therefore, focused on behavior modifications to reduce caloric intake and increase physical activity using a myriad of systems. These methods have limited efficacy and are associated with recidivism rates exceeding 95% (NIH Technology Assessment Conference Panel, Ann. Intern. Med. 119:764-770, 1993).

Obesity has also been treated by administering specific agents, for example, anorectic agents, to obese subjects. However, anorectic agents such as dextroamphetamine, the combination of the non-amphetamine drugs phentermine and fenfluramine (Phen-Fen), and dexfenfluramine

(Redux) alone, are associated with serious side effects. Indigestible materials such as olestra (OLEAN®, mineral oil or neopentyl esters (see U.S. Pat. No. 2,962,419)) have been proposed as substitutes for dietary fat. Garcinia acid and derivatives thereof have been described as treating obesity by interfering with fatty acid synthesis. Swellable crosslinked vinyl pyridine resins have been described as appetite suppressants via the mechanism of providing non-nutritive bulk (*see, e.g.*, U.S. Pat. No. 2,923,662).

Surgical interventions, such as gastric partitioning procedures, jejunoileal bypass, and vagotomy, have also been developed to treat severe obesity (Greenway, Endo. Metab. Clin. N. Amer. 25:1005-1027, 1996). Although these surgical procedures are somewhat more effective in the long run, the acute risk benefit ratio has reserved these invasive procedures for morbidly obese patients according to the National Health Institutes (NIH) consensus conference on obesity surgery (BMI>40 kg/m^2) (NIH Conference, Ann. Intern. Med. 115:956-961, 1991). Therefore, this approach is not an alternative for the majority of overweight patients unless and until they become profoundly obese and are suffering the attendant complications.

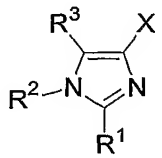
Thus, new methods and compositions that promote weight-loss are urgently needed.

SUMMARY OF THE INVENTION

The present invention provides substituted imidazole derivatives which have been found to suppress appetite and induce weight loss in laboratory animals. The invention also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to substituted imidazole derivatives that have utility in the treatment of obesity, said derivatives having Formula I



(I)

wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl sulfonyl, (C_1–C_6)alkyl sulfonyl-amino, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl,

(C_2–C_6)alkyl,

cyclohexyl optionally substituted with (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

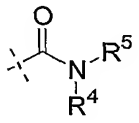
1-naphthyl or 2-naphthyl optionally substituted with halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen or (C_1–C_6)alkyl;

R^5 is selected from

(C_2–C_9)alkyl or (C_7–C_{11})bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C_1–C_6)alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C_1–C_6)alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, (C_1–C_3)alkoxy-substituted (C_1–C_3)alkyl, benzyl, or phenyl optionally substituted with one or more of (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

$-NR^6R^7$

where R^6 is hydrogen or (C_1–C_6)alkyl;

R^7 is (C_1–C_9)alkyl; or phenyl optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, (C_1–C_3)alkoxy-substituted (C_1–C_3)alkyl, phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

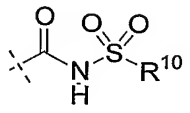
R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C_1–C_6)alkyl, (C_1–C_6)alkoxy, hydroxy-substituted (C_1–C_3)alkyl, (C_1–C_3)alkoxy-substituted (C_1–C_3)alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, cyano, a 5- to 10-

membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or

X is 

where R^{10} is (C_1–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

Another embodiment of the invention consists of imidazole derivatives having Formula I wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1-C_6)alkyl carbonyl-amino, (C_1-C_6)alkyl amino-carbonyl-amino, or phenyl,

(C_2–C_6)alkyl,

cyclohexyl optionally substituted with (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

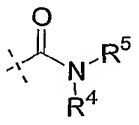
1- or 2-naphthyl optionally substituted with halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or phenyl, with the proviso that R^2 is not an unsubstituted 4-pyridyl or an unsubstituted 4-pyrimidinyl group;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

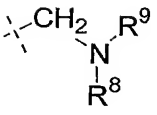
X is 

where R^4 is hydrogen or (C_1–C_6)alkyl;

R^5 is phenyl substituted with one or more (C_1-C_6)alkyl, hydroxy (C_1-C_6)alkyl, (C_1-C_6)alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more (C_1–C_6)alkyl, (C_1–C_6)alkoxy, or trifluoromethyl;

or

X is 

where R^8 is a hydrogen or (C_1–C_6)alkyl;

R^9 is a $(C_1–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl group, each of which is optionally substituted with one or more of phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or fluorine,

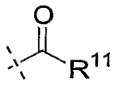
benzyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or halogen;

or

R^8 and R^9, together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of $(C_1–C_6)$alkyl, benzyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or

X is 

where R^{11} is $(C_2–C_9)$alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or fluorine,

phenyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy $(C_1–C_6)$alkyl, and optionally substituted on the phenyl ring with halogen,

(C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

The terms identified above have the following meaning throughout:

"Halogen" means fluorine, chlorine, bromine or iodine.

The terms "(C_1–C_3)alkyl", "(C_1–C_6)alkyl", "(C_2–C_6)alkyl", "(C_1–C_9)alkyl", and "(C_2–C_9)alkyl" mean C_1–C_3, C_1–C_6, C_2–C_6, C_1–C_9, and C_2–C_9 linear or branched alkyl groups, respectively, that may also include a cyclic alkyl radical as part of the alkyl group. For example, this includes groups such as cyclopropyl, cyclohexyl, cyclopropyl-methyl, and cycloheptyl-methyl groups. The preferred alkyl groups are methyl, ethyl, propyl, and isopropyl groups.

"(C_1–C_3)alkoxy" and "(C_1–C_6)alkoxy" mean (C_1–C_3)alkyl-oxy and (C_1–C_6)alkyl-oxy, respectively.

"(C_7–C_{11})bicycloalkyl" means a C_7–C_{11} bicyclic alkyl group, such as octahydro-2-pentalenyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[3.2.1]oct-8-yl, that is optionally substituted with one or more methyl groups.

The term "5- to 10-membered saturated or unsaturated heterocyclic radical" means a fused or bridged, mono-, bi-, or tri-cyclic, non-aromatic heterocyclic radical which may contain one to three of the heteroatoms nitrogen, oxygen, or sulfur. These radicals include the following radicals, for example, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, azepan-1-yl, morpholin-4-yl, hexahydrocyclopenta[c]pyrrol-2(1H)-yl, and thiomorpholin-4-yl.

The term "5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical" means a 5- or 6-membered aromatic heterocyclic radical or a fused bicyclic aromatic heterocyclic radical, which may contain one to three of the heteroatoms nitrogen, oxygen, or sulfur. These radicals include the following radicals, for example, furyl, thienyl, isoxazolyl, pyridyl, pyrimidinyl, benzofuranyl, and benzothienyl.

When any moiety is described as being substituted, it can have one or more of the indicated substituents that can be located at any available position on the moiety. When there are two or more substituents on any moiety, each term shall be defined independently of any other in each occurrence.

Representative salts of the compounds of Formula I include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic

acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine salts and *N*-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The esters in the present invention are non-toxic, pharmaceutically acceptable ester derivatives of the alcohols of Formula I. This includes ester derivatives prepared from acetic, benzoic, mandelic, stearic, lactic, salicylic, hydroxynaphthoic, glucoheptonic, and gluconic acid. The alcohol compounds of Formula I may be esterified by a variety of conventional procedures including reacting the appropriate anhydride, carboxylic acid, or acid chloride with the alcohol group of the Formula I compound. The appropriate anhydride is reacted with the alcohol in the presence of an acylation catalyst such as 1,8-bis[dimethylamino]naphthalene or DMAP (*N,N*-dimethylaminopyridine). An appropriate carboxylic acid may be reacted with the alcohol in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide or other water soluble dehydrating agents which are used to drive the reaction by the removal of water, and optionally, an acylation catalyst. Esterification may also be reached using the appropriate carboxylic acid in the presence of trifluoroacetic anhydride and optionally, pyridine, or in the presence of *N,N*-carbonyldiimidazole with pyridine. Reaction of an acid chloride with the alcohol may be carried out with an acylation catalyst such as DMAP or pyridine. One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification of alcohols. Sensitive or reactive groups on the compound of Formula I may need to be protected during any of the above methods for forming esters, and protecting groups may be added and removed by conventional methods well known in the art.

It will be appreciated that diastereomers and enantiomers of the exemplified structures will often be possible, and that pure isomers represent preferred embodiments. It is intended that pure stereoisomers, and mixtures thereof, are within the scope of the invention.

The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers. Any isomer may be present in the (*R*)-, (*S*)-, or (*R,S*) configuration, preferably in the (*R*)- or (*S*)- configuration, whichever is most active.

All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

Geometric isomers by nature of substituents about a double bond or a ring may be present in cis (= *Z*-) or trans (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific moieties and the specific substituents on the various moieties, all play a role in the path to be followed in the preparation of the specific compounds of this invention. These factors are readily recognized by one of ordinary skill in the art.

For synthesis of any particular compound, one skilled in the art will recognize that the use of protecting groups may be required for the synthesis of compounds containing certain substituents. A description of suitable protecting groups and appropriate methods of adding and removing such groups may be found in: Protective Groups in Organic Synthesis, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

In the Reaction Schemes below, one skilled in the art will recognize that reagents and solvents actually used may be selected from several reagents and solvents well known in the art to be effective equivalents. When specific reagents or solvents are shown in a Reaction Scheme, therefore, they are meant to be illustrative examples of conditions desirable for the execution of that particular Reaction Scheme. Abbreviations not identified in accompanying text are listed later in this disclosure under "Abbreviations and Acronyms."

Another object of this invention is to provide methods of making the compounds of the invention. The compounds may be prepared from readily available materials by the methods outlined in Reaction Schemes 1 and 2 below, and by obvious modifications thereto.

The present invention relates to the use of the compounds of this invention for the treatment of bulimia and obesity including associated dyslipidemia and other obesity- and overweight-related complications such as, for example, cholesterol gallstones, cancer (e.g., colon,

rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, and bile duct), menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea, as well as for a number of other pharmaceutical uses associated therewith, such as the regulation of appetite and food intake, dyslipidemia, hypertriglyceridemia, Syndrome X, type II diabetes (non-insulin-dependent diabetes), atherosclerotic diseases such as heart failure, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease and peripheral vessel disease. The compounds of this invention may also be useful for treating physiological disorders related to, for example, regulation of insulin sensitivity, inflammatory response, plasma triglycerides, HDL, LDL and cholesterol levels and the like.

The compounds of Formula I of this invention are expected to be valuable as therapeutic agents. Accordingly, an embodiment of this invention includes a method of treating the various conditions identified above in a patient (including mammals) which comprises administering to said patient a composition containing an amount of the compound of Formula I that is effective in treating the target condition.

Compounds of Formula I may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula I and one or more additional therapeutic agents, as well as administration of the compound of Formula I and each additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula I and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

Where separate dosage formulations are used, the compound of Formula I and one or more additional therapeutic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

For example, the compounds of Formula I may be used in combination with other therapies and drugs useful for the treatment of obesity, for example, in combination with β_3-adrenoreceptor agonists such as CL-316,243, or in combination with a drug compound that modulates digestion and/or metabolism such as drugs that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

In addition, the compounds of Formula I may be administered in combination with one or more of the following hypoglycemic agents for the treatment of diabetes or diabetes-related disorders: insulin; biguanidines such as metformin or buformin; sulfonylureas such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glipizide, glyclazide; or any

other insulin secretagogue such as, for example, repaglinide and nateglinide; or α-glycosidase inhibitors such as acarbose, voglibose, or miglitol. Also, the compounds of Formula I may be used in combination with HMG Co-A reductase inhibitors (statins), bile acid binding resin, or fibric acid derivatives to improve the lipid profile of subjects with dyslipidemia. Compounds of Formula I may also be used in combination with agents that regulate hypertension (e.g., inhibitors of angiotension converting enzyme (ACE), β-blockers, calcium channel blockers).

Furthermore, compounds of the present invention were determined, following oral dosing in rodents, to be present in significant concentrations in the brain. Therefore, the compounds of this invention may have utility for the treatment of any of various CNS (central nervous system) or psychological disorders, such as the treatment of substance or behavioral addiction, and the treatment of disorders associated with the use of psychotropic substances. Likewise, the compounds of this invention may have utility for the management and treatment of cognition and memory disorders.

The compounds of Formula I may also be utilized, in free base form or in compositions, as well as in research and diagnostics or as analytical reference standards, and the like, which are well known in the art. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound of Formula I, or a salt, or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of the compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

It is anticipated that prodrug forms of the compounds of this invention will prove useful in certain circumstances, and such compounds are also intended to fall within the scope of the invention. Prodrug forms may have advantages over the parent compounds exemplified herein, in that they are better absorbed, better distributed, more readily penetrate the central nervous system, are more slowly metabolized or cleared, etc. Prodrug forms may also have formulation advantages in terms of crystallinity or water solubility. For example, compounds of the invention having one or more hydroxyl groups may be converted to esters or carbonates bearing one or more carboxyl, hydroxyl or amino groups, which are hydrolyzed at physiological pH values or are cleaved by endogenous esterases or lipases *in vivo*. See for example U.S. Patent Nos. 4,942,184; 4,960,790; 5,817,840; and 5,824,701 (all of which are incorporated herein by reference in their entirety), and references therein.

An object of this invention is to provide a method of inducing weight loss in an individual by administration of a compound of the invention. The method of the invention comprises administering to an individual a therapeutically effective amount of at least one compound of the

invention, or a prodrug thereof, which is sufficient to induce weight loss. The invention further comprises a method of preventing weight gain in an individual by administering an amount of at least one compound of the invention, or a prodrug thereof, which is sufficient to prevent weight gain.

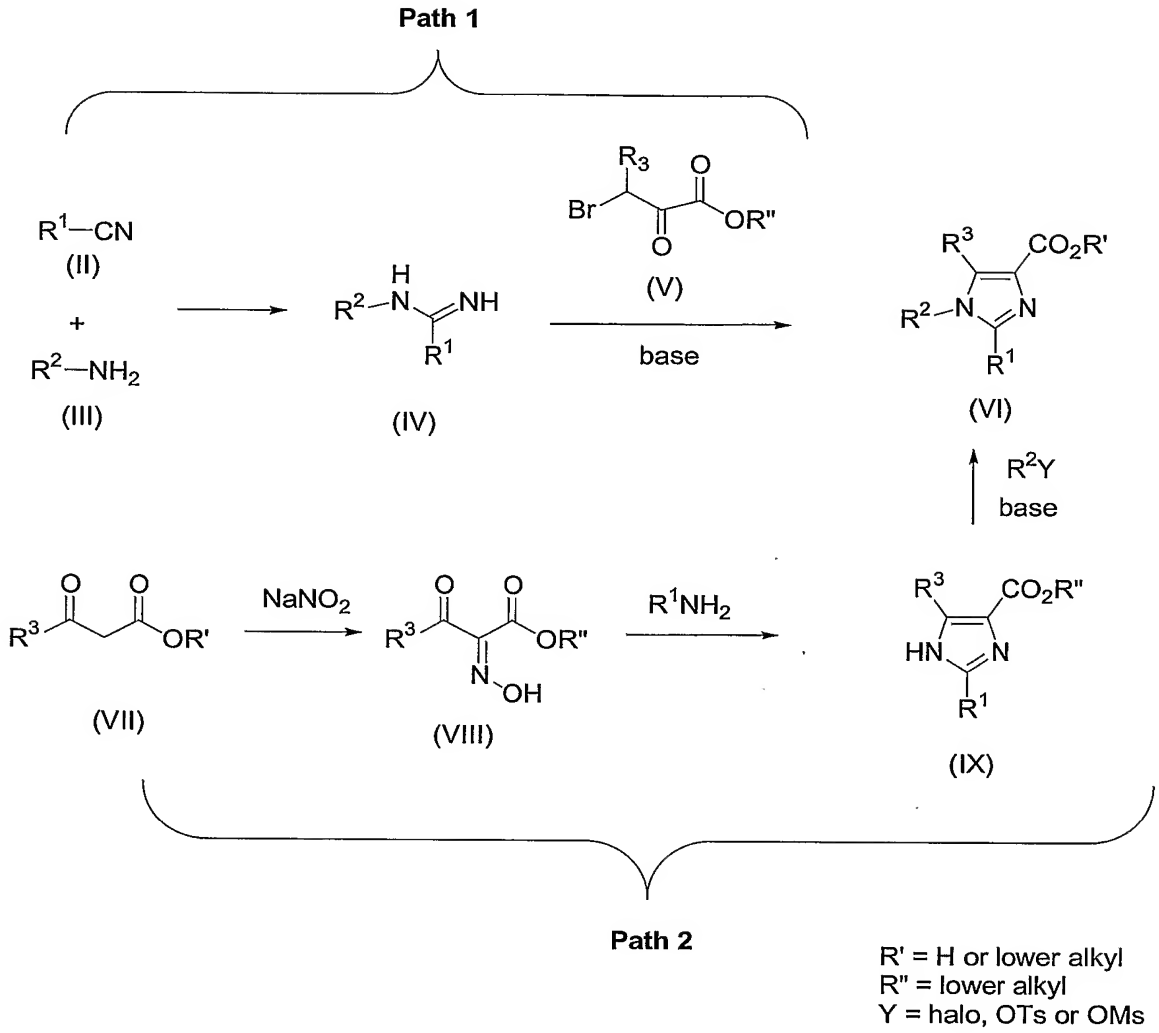
5

General Preparation of Compounds of Formula I

Compounds of Formula I are prepared by a variety of methodologies. The selection of the particular method to be used depends upon such factors as the availability of appropriate starting materials, compatibility of functional groups with the reagents used, and the ultimate structural 10 features present in the final compound being prepared. It will be understood by those skilled in the art that more than one method may, in some cases, be useful for the preparation of individual compound examples of Formula I.

In general, the compounds of Formula I are prepared from the intermediate compound of Formula VI by the methods outlined in Reaction Scheme 2; the compound of formula VI is 15 prepared by the methods outlined in Reaction Scheme 1, by one of the two paths as shown. For the compounds of Formulas Ia-d and II-XIII, unless specifically defined otherwise, R, R^1-R^{11}, and X are as defined above for Formula I.

Reaction Scheme 1



Preparation of Intermediates of Formula VI (Reaction Scheme 1)

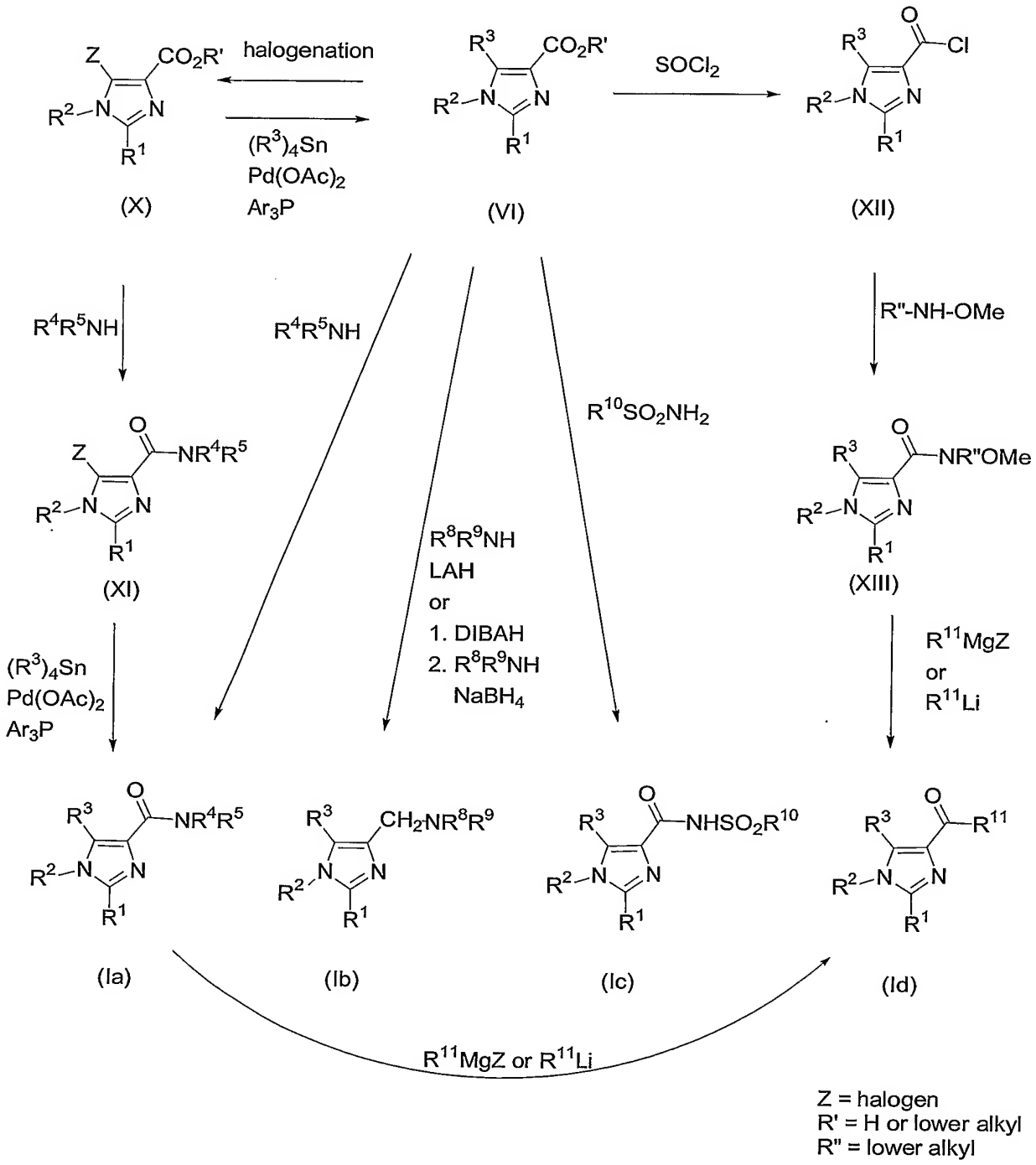
In Path 1, an imidamide of Formula IV is prepared by reaction of an amine of Formula III with a nitrile of Formula II. This reaction is either conducted using a strong base such as a Grignard reagent (e.g., EtMgBr) in a neutral solvent (e.g., THF) at room temperature, or with a Lewis Acid (e.g., $AlCl_3$) in an inert solvent (e.g., toluene) with heating. The product, imidamide IV, is then allowed to react with a 3-bromopyruvate of Formula V by mixing together in an inert solvent (e.g., toluene or THF), with optional heating, to give the imidazole intermediate of Formula VI. This reaction may be further facilitated by the addition of a base (e.g., propyl amine, sodium carbonate, and the like) to remove excess HBr produced as a side product. Alternatively, the conversion of IV to VI may be accomplished in a stepwise manner, i.e., first carrying out the

reaction of IV with V and isolation of the crude product, and then heating the residue with the R^1NH_2 compound in acetic acid complete the cyclization to imidazole VI.

In path 2, ketoesters of Formula VII are converted to an oxime compound of Formula VIII, by reaction with sodium nitrite in a protic solvent, typically acetic acid/water, while cooling. The product VIII is then heated with an amine of formula R^1NH_2 in a polar solvent such as acetonitrile, to provide the imidazole of Formula IX. Finally, N-substitution may be carried out by treatment of IX with a base and a compound of formula R^2Y, where Y is a leaving group such as halogen, mesylate, or tosylate. For this pathway, when the R^2 is aryl, it is generally an activated (electrophilic) haloarene such as 4-halonitrobenzene or a 2- or 4-halopyridine, capable of undergoing nucleophilic aromatic substitution reactions.

The compounds of Formula VI, in which R' is H, may be made from the compounds of Formula VI in which R' is alkyl, by ester hydrolysis methods well known in the art.

Reaction Scheme 2



Preparation of Compounds of Formula I (Reaction Scheme 2)

The compounds of Formula VI, prepared as shown in Reaction Scheme 1, may then be used for the preparation of the compounds of Formula I. To illustrate the methods which are useful for the preparation of the Formula I compounds, synthetic routes are shown for the more

specific compounds of Formula Ia, Ib, Ic, and Id. These four structures represent the variants of the Formula I compounds when X = $-C(=O)NR^4R^5$, $-CH_2NR^8R^9$, $-C(=O)NHSO_2R^{10}$, and $-C(=O)R^{11}$, respectively.

The synthetic methods for the preparation of each of these variants of the Formula I compounds are illustrated in Reaction Scheme 2.

In one such method, compounds of Formula VI, in which R' = H, the carboxylic acid group is first activated as an acid halide (e.g., using $SOCl_2$ or TFFH) and subsequently treated with a compound of formula R^4R^5NH, usually with base present such as triethyl amine or PS-DIEA (polystyrene bound-diisopropylethylamine). Alternatively, the acid may be activated as a carbodiimide adduct (e.g., with 1-(3-dimethylaminopropyl, triethylamine, and 1-hydroxy-7-azabenzotriazole)-3-ethylcarbodiimide hydrochloride) or as a hexafluorophenyl ester (prepared from hexafluorophenol and EDCI). Following activation, a compound represented as R^4R^5NH is added to complete the reaction to the Formula Ia compound. One-pot variations of this conversion may also be carried out, for example, by mixing a coupling reagent such as HATU and the R^4R^5NH compound at the same time.

Compounds of Formula Ia may also be prepared from compounds of Formula VI where R' = alkyl by heating together the R^4R^5NH compound and trimethylaluminum.

Compounds of Formula Ia may also be prepared as shown, from an ester of Formula VI where R^3 is H, by first halogenating the imidazole by standard means (e.g., NBS or SO_2Cl_2) to give the haloimidazole of Formula X. While this intermediate may be used to prepare Formula VI intermediates where $R^3 \neq H$, using such methods as Pd-catalyzed organotin coupling reactions (e.g., when R^3 is methyl), Formula X compounds may also be converted to the amides of Formula XI under the same conditions described above for conversion of Formula VI compounds to Formula IA. The resulting amide of Formula XI may then be converted to a Formula Ia compound, where $R^3 \neq H$, by Pd-catalyzed organotin coupling reactions.

Formula Ib compounds may be prepared from Formula VI compounds in the presence of an amino compound of Formula R^8R^9NH under reductive conditions. When R^8 is hydrogen, a Formula VI compound where R' = alkyl, is first partially reduced to the aldehyde with, for example, diisobutylaluminum hydride (DIBAH), the R^8R^9NH compound is added to form an imine intermediate in situ, which is then reduced with sodium borohydride. When $R_8 \neq H$, the reductive alkylation may be accomplished in one step with the R^8R^9NH compound and lithium aluminum hydride by using the procedure described by Khanna et al., (Synthesis 607-608, 1975).

The acylsulfonamides of Formula Ic may be prepared by reaction of the Formula VI compound (where R' = H) with a sulfonamide of Formula $R^{10}SO_2NH_2$, facilitated by a coupling

agent such as, for example, a *N,N'*-dialkyl carbodiimide such as *N,N'*-dicyclohexyl carbodiimide and a base such as, for example, DMAP.

Formula Id compounds may be prepared by conversion of an acid chloride represented by Formula XII, prepared as described above from VI (where R' = H) and $SOCl_2$, to an amide of Formula XIII, which is then allowed to undergo reaction with a organometallic reagent such as, for example, an alkyl or aryl Grignard reagent of Formula $R^{11}MgBr$, prepared by standard methods. The resulting product is the ketone of Formula Id. This Formula Id ketone may also be prepared by similar reaction of aryl- or alkllithium reagents, such as, for example, $R^{11}Li$, with Formula XIII, or certain Formula Ia amides where R^4R^5NH is 4-piperidone.

Conversion of the substituted compounds of Formula Ia, Ib, Ic, and Id to differently substituted Formula I compounds may be carried out using standard functional group conversion chemistry. For example, keto substituents may be reduced with reagents such as Na_2BH_4, to the corresponding hydroxy substituted compounds. Other such examples are 1) the conversion of nitrophenyl substituent to the corresponding aminophenyl substituent, and 2) O- or N-alkylation or acylation of OH or NH substituents to give the corresponding O- or N-alkyl or O- or N-acyl substituted compounds.

EXPERIMENTAL EXAMPLES

The following specific preparative examples are included as illustrations of preparation of specific compounds of the invention, and are not to be construed as limiting the scope of the invention in any way.

NMR methods:

Proton (^1H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric G*N*-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as reference standard. Carbon (^{13}C) NMR spectra were measured with a General Electric G*N*-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; d_3-MeOD; δ 49.0; d_6-DMSO δ 39.5) as reference standard.

LC-MS instrumentation:

(a) a Gilson HPLC system equipped with two Gilson 306 pumps, a Gilson 215 Autosampler, a Gilson diode array detector, a YMC Pro C-18 column (2 x 23mm, 120 A), and a Micromass LCZ single quadrupole mass spectrometer with z-spray electrospray ionization. Spectra were scanned from 120-800 amu over 1.5 seconds. ELSD (Evaporative Light Scattering Detector) data was also acquired as an analog channel.

(b) a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source.

HPLC conditions. In the Examples and Tables provided below, LC-MS data are given with retention times (RT) determined by using one of the following methods:

Method 1. Eluents were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonitrile with 0.02% TFA. Elution conditions consisted of a flow rate of 1.0 mL/min with an initial hold at 10% B for 0.5 minutes, followed by gradient elution from 10% B to 95% B over 3.5 minutes, followed by a final hold at 95% B for 0.5 minutes. Total run time was 6.5 minutes.

Method 2. Eluents as above; elution at a flow rate of 1.5 mL/min with an initial hold at 10% B for 0.5 minutes, followed by gradient elution from 10% B to 90% B over 3.5 minutes, followed by a final hold at 90% B for 0.5 minutes. Total run time was 4.8 minutes.

Abbreviations and Acronyms

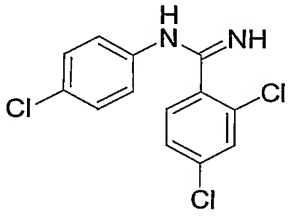
When the following abbreviations are used herein, they have the following meaning:

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CD_3OD	methanol-d_4
Celite®	diatomaceous earth filter agent, ®Celite Corp.
DMAP	4-(*N,N*-dimethylamino)pyidine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ELSD	evaporative light scattering detector
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography-mass spectroscopy
min	minute(s)

m/z	mass-to-charge ratio
MeCN	acetonitrile
Ms	methanesulfonyl
NBS	N- bromosuccinimide
NMM	4-methylmorpholine
OMs	methanesulfonyl-oxy
OTs	4-toluenesulfonyl-oxy
PS-DIEA	Polystyrene-bound diisopropylethylamine
Rf	retention factor (TLC)
RT	retention time (HPLC)
rt	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFFH	Fluoro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate
TLC	thin layer chromatography
Ts	4-toluenesulfonyl

Example 1

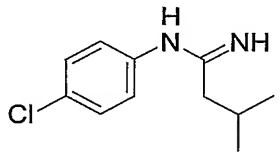
Preparation of 2,4-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide



Under argon, 4-chloroaniline (6.67 g, 52.5 mmol) was slowly added to EtMgBr (52 mL, 1 M in THF, 52 mmol) portion wise. After the solution was stirred for 0.5 h, 2,4-dichlorobenzonitrile (9.03 g, 52.5 mmol) was added. The resulting solution was stirred at rt overnight. The reaction mixture was carefully quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Crude product (16.26 g,) was obtained as a sticky brown foam which was used without purification for the next step. LC-MS *m/z* 299.3 (MH^+), retention time 1.75 min (MDLC 1); ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (2H, br), 7.09-7.51 (7H, m).

Example 2

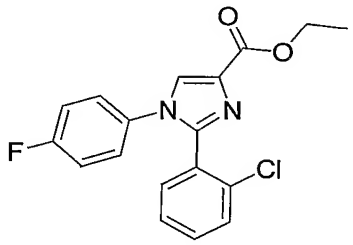
Preparation of *N*-(4-chlorophenyl)-3-methylbutanimidamide



To a solution of 3-methylbutanenitrile (250 mg, 3.0 mmol) and $AlCl_3$ (400 mg, 3.0 mmol) in toluene (6 mL) was added 4-chloroaniline (383 mg, 3.0 mmol). The resulting solution was stirred at reflux for 2 h, diluted with water, and extracted with EtOAc. The aqueous layer was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product (364 mg, 58% yield) was used for the next step without purification.

Example 3

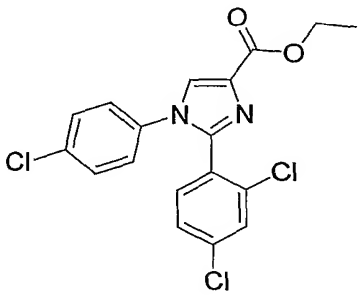
Preparation of ethyl 1-(4-fluorophenyl)-2-(2-chlorophenyl)-1*H*-imidazole-4-carboxylate



To a solution of crude 2-chloro-*N*-(4-fluorophenyl)benzenecarboximidamide (6.8 g, 27 mmol) in toluene (100 mL), ethyl bromopyruvate (3.5 mL, 27 mmol) was added. The resulting solution was heated at 115°C for 90 minutes. The reaction mixture was cooled to rt. Propylamine (2.2 mL, 27 mmol) was added. The reaction mixture was diluted with ethyl acetate and washed with saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (30 % ethyl acetate in hexane) to give the product (3.4 g, 37% overall yield from 4-fluoroaniline) as a light yellow solid: LC-MS *m/z* 345.2 (MH^+), retention time 2.78 min (method 1); Rf = 0.20 (30% EtOAc in hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 1.38-1.43 (3H, t, J = 6.9 Hz), 4.39-4.46 (2H, q, J = 3.9 Hz), 6.98-7.52 (8H, m), 7.89 (1H, s).

Example 4

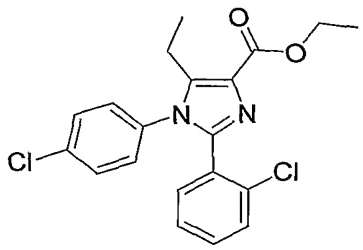
Preparation of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate



To a solution of crude 2,4-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide (10.3 g, 34.6 mmol) in toluene (100 mL), ethyl bromopyruvate (4.3 mL, 34.6 mmol) and Na_2CO_3 (7.3 g, 41.6 mmol) were added. The resulting solution was heated at reflux for 3 h. The reaction mixture was cooled to rt. The solid was filtered off and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (40 % ethyl acetate in hexane) to give the product (7.5 g, 52% overall yield from 4-chroloaniline) as a light yellow solid: LC-MS *m/z* 395 (MH^+), retention time 3.91 min (method 1); mp 143-144°C; Rf = 0.63 (50% EtOAc in hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 1.39-1.43 (3H, t, J = 7.2 Hz), 4.39-4.46 (2H, q, J = 6.9 Hz), 7.04-7.08 (2H, m), 7.25-7.50 (5H, m), 7.89 (1H, s).

Example 5

Preparation of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazole-4-carboxylate

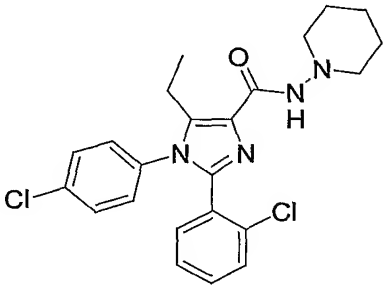


A solution of 2-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide (10 g, 37.7 mmol) in THF (100 mL) was treated with K_2CO_3 (5.2g, 37.7 mmol) followed by the slow addition of ethyl 3-bromo-2-oxopentanoate (10.1 g, 45 mmol) over 3 h. The reaction mixture was stirred at rt overnight. The solid was then filtered off and the solvent was evaporated. The residue (20 g, 37.7 mmol) was dissolved in acetic acid (100 mL) and heated at reflux for 1 h. The reaction mixture

was cooled to rt, diluted with water (200 mL), and extracted with ethyl acetate. The organic layer was washed with water. The aqueous layer was neutralized with saturated $NaHCO_3$, and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (40% ethyl acetate in hexane) to give the product (8.5 g, 40% overall yield from 4-chroloaniline) as a light yellow solid: LC-MS *m/z* 389 (MH^+), retention time 3.31 min (method 1); Rf = 0.28 (40% EtOAc in hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.10 (3H, t, J = 7.5 Hz), 1.40-1.44 (3H, t, J = 7.2 Hz), 2.85-2.92 (2H, q, J = 4.2 Hz), 4.39-4.46 (2H, q, J = 7.2 Hz), 7.09-7.41(8H, m).

Example 6

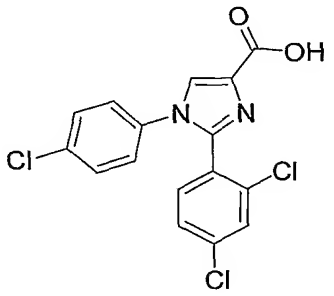
Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide



To a solution of 1-aminopiperidine (2.48 mL, 23 mmol) in CH_2Cl_2 (15 mL) was added trimethylaluminum (11.5 mL, 2 M in hexane, 23 mmol). After the mixture was stirred for 0.5 h, a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazole-4-carboxylate (3.0 g, 7.7 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was heated at reflux for 2 h and cooled to rt. Water was slowly added dropwise to the reaction mixture at 0°C until no more gas bubbled out. The mixture was dried over Mg_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (40 % then 60% ethyl acetate in hexane) to give the product (2.4 g, 64 % yield) as a white solid: LC-MS *m/z* 443 (MH^+), retention time 2.95 min (method 1); mp 208-209 °C; Rf = 0.74 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$) δ 0.98-1.03 (3H, t, 7.8 Hz), 1.35-1.37 (2H, m), 1.58-1.70 (4H, m), 2.77-2.88 (6H, m), 6.70-7.30 (8H, m), 7.84 (1H, s).

Example 7

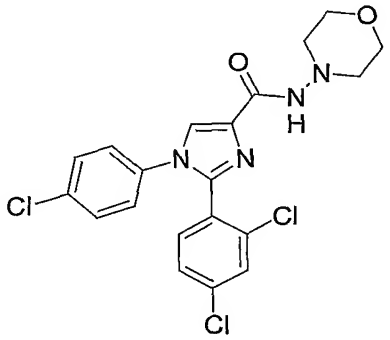
Preparation of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5*H*-imidazole-4-carboxylic acid



To a solution of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (1.1 g, 2.79 mmol) in MeOH (20 mL), a solution of KOH (2.2 g, 39 mmol) in H_2O (20 mL) was added. The mixture was heated at 90°C for 3 h. The reaction mixture was cooled to rt and the MeOH was evaporated. HCl (1N) was added until a white precipitate formed. The solid was filtered off, and dried under vacuum. The product (1.0 g, 98% yield) was obtained as a white solid: LC-MS *m/z* 367 (MH^+), retention time is 3.43 min (method 1); mp 150-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.65 (7H, m), 8.26 (1H, s).

Example 8

Preparation of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(4-morpholinyl)-1*H*-imidazole-4-carboxamide

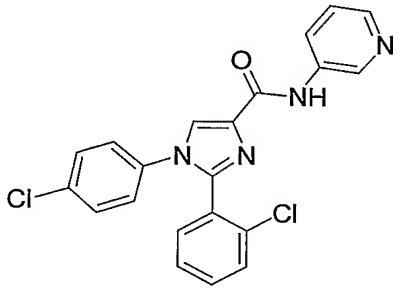


To a solution of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5*H*-imidazole-4-carboxylic acid (50 mg, 0.137 mmol) in CH_2Cl_2 (5 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58 mg, 0.164 mmol), 1-hydroxy-7-azabenzotriazole (40 mg, 0.164 mmol), and triethylamine (1.5 mL) were added. After the mixture was stirred for 15 minutes, 4-morpholinamine (0.164 mmol) was added. The reaction mixture was stirred at rt overnight, and

washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by HPLC (YMC-packed PRO C18 15 x 200 mm column, 10-90% CH_3CN in H_2O/TFA, 20 mL/min.) to give the product (10 mg, 16% yield) as a yellow oil: LC-MS *m/z* 451 (MH^+), retention time 3.03 min (method 1); Rf = 0.57 (50% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 2.97-3.00 (4H, t, J = 4.5 Hz), 3.83 – 3.86 (4H, t, J = 4.2 Hz), 7.04 – 7.39 (8H, m), 7.92 (1H, s).

Example 9

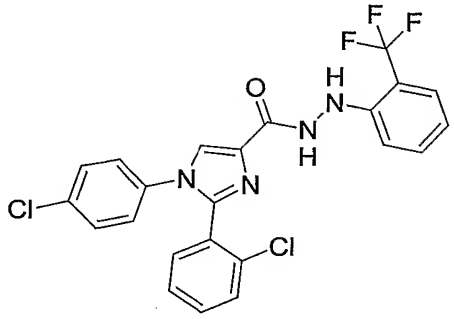
Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(3-pyridinyl)-1*H*-imidazole-4-carboxamide



2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (403 mg, 1.2 mmol) was dissolved in dichloromethane (5 mL) and treated with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (459 mg, 1.56 mmol) and *N*-methylmorpholine (NMM) (182 mg, 1.8 mmol). The mixture was stirred under argon for 15 minutes before 3-aminopyridine (349 mg, 3.6 mmol) was added. Stirring at rt was continued overnight. The reaction mixture was then adsorbed onto silica gel and chromatographed (2-3% MeOH in CH_2Cl_2) to afford 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(3-pyridinyl)-1*H*-imidazole-4-carboxamide (266 mg, 54% yield): LC-MS *m/z* 409.3, retention time 2.43 min (method 1).

Example 10

Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N'*-[2-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide

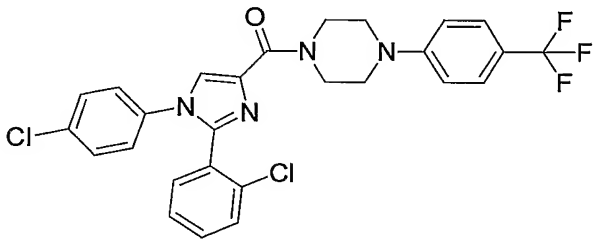


In a 20-mL screw-cap vial, 100 mg (0.3 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid, 87 mg (0.33 mmol) TFFH (Advanced Chemtech, Louisville, KY), and 5.0 equiv. PS-DIEA (Argonaut Technologies Inc., San Carlos, CA) (loading level: 3.50 mmol/g, 429 mg, 1.5 mmol) were heated in 8 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (58 mg, 0.33 mmol) 2-(trifluoromethyl)phenyl hydrazine was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 41.8 mg of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide as the trifluoroacetate salt (light yellow solid, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 7.85 (s, 1 H), 7.45 (m, 2 H), 7.20-7.38 (m, 6 H), 7.12 (d, 1 H), 7.00 (d, 2 H), 6.88 (t, 1 H), 6.60 (s, 1 H); LC-MS *m/z* 491.2 (MH^+), retention time 4.02 min (method 2).

The free base form of the product was obtained by dissolving the TFA salt in dichloromethane, washing with saturated aqueous sodium carbonate solution and water, followed by drying the organic phase with magnesium sulfate, and evaporation of the organic phase under reduced pressure. The hydrochloride salt form of the product was obtained by treating the free base in dichloromethane with 1.0 M hydrogen chloride in diethyl ether until no more precipitate was formed, followed by evaporation of solvent under reduced pressure.

Example 11

Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl) phenyl]piperazine

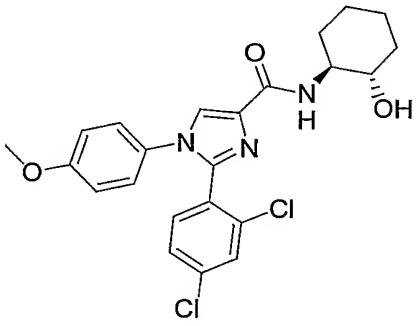


In a 20-mL screw-cap vial, 100 mg (0.3 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid, 87 mg (0.33 mmol) TFFH, and 5.0 equiv. PS-DIEA (loading level: 3.50 mmol/g, 429 mg, 1.5 mmol) were heated in 8 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (76 mg, 0.33

mmol) 1-(4-trifluormethylphenyl)-piperazine was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 45.9 mg of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine as the trifluoroacetate salt (yellow oil, 23% yield). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.95 (s, 1 H), 7.60 (m, 1 H), 7.30-7.50 (m, 7 H), 7.25 (d, 2 H), 7.05 (d, 2 H), 4.5 (bs, 2 H), 3.80 (bs, 2 H), 3.35 (m, 4 H); LC-MS *m/z* 545.3 (MH^+), retention time 4.21 min (method 2).

Example 12

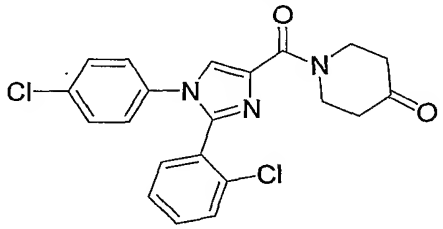
2-(2,4-dichlorophenyl)-*N*-(trans-2-hydroxycyclohexyl)-1-(4-methoxyphenyl)-1*H*-imidazole-4-carboxamide



In a 20-mL screw-cap vial, 182 mg (0.5 mmol) 2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-imidazole-4-carboxylic acid, 145 mg (0.55 mmol) TFFH, and 5.0 equiv. PS-DIEA (loading level: 3.50 mmol/g, 716 mg, 2.5 mmol) were heated in 10 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (84 mg, 0.55 mmol) trans-2-aminocyclohexanol hydrochloride was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 53 mg of 2-(2,4-dichlorophenyl)-*N*-(trans-2-hydroxycyclohexyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide (amber oil, 23% yield). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.90 (s, 1 H), 7.30-7.50 (m, 4 H), 7.10 (d, 2 H), 6.90 (d, 2 H), 3.85 (s, 3 H), 3.80 (m, 1 H), 3.50 (m, 1 H), 3.25 (bs, 1 H), 2.0 (m, 2 H), 1.75 (m, 2 H), 1.30-1.50 (m, 4 H); LC-MS m/z 460.2 (MH^+), retention time 3.31 min (method 2).

Example 13

Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone

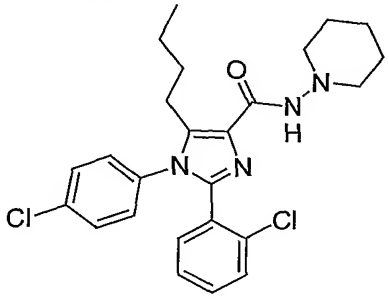


Step 1. Thionyl chloride (0.66 mL, 9 mmol) was added to a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (1 g, 3 mmol) in toluene (10 mL). The mixture was refluxed under argon for 1.5 h and concentrated to provide 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride, which was used in the next step without purification. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.40 (s, 1H), 7.69-7.09 (m, 8H).

Step 2. Triethylamine (1.46 mL, 10.45 mmol) was added to a suspension of 4-piperidinone trifluoroacetate (0.76 g, 3.58 mmol) in CH_2Cl_2 (10 mL) and a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride in CH_2Cl_2 (5 mL) was added. The mixture was stirred at rt under argon for 17 h, diluted with CH_2Cl_2 (50 mL), washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated to give 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone as a yellow solid (0.96 g, 77 %). MS (Electrospray) 414 (MH^+), ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.80 (s, 1H), 7.37-7.20 (m, 6H), 7.06-7.00 (m, 6H), 4.47 (br, 2H), 3.92 (br, 2H), 2.46 (t, 4H).

Example 14

5-Butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide



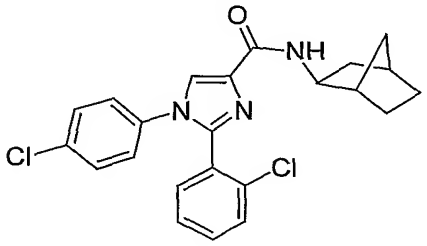
Step 1. To a solution of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (438 mg, 1.12 mmol) in dry toluene (3 mL), at rt was added thionyl chloride (401 μL, 3.4 mmol). The solution was stirred overnight at rt, and then heated at 110°C for 5 h.

The resulting reaction was cooled to rt, and the solvents evaporated, to give 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride (455 mg, 100%), which was used in the next step without purification. LC-MS *m/z* 407 (MH^+), retention time 3.62 min (method 2).

Step 2. To a solution of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride (227 mg, 0.56 mmol) in CH_2Cl_2 (5 mL), were added 1-aminopiperidine (113 mg, 1.12 mmol) and Et_3N (234 μL, 1.68 mmol). The solution was stirred overnight at rt, and then the solvents were evaporated under reduced pressure. The residue was purified by preparative reversed-phase HPLC, using 20 to 100% MeCN in water as gradient, to provide 125 mg (48 %) of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide as a white powder. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.27 (m, 8 H), 2.93 (t, 2 H), 2.82 (bs, 4 H), 1.77-1.71 (m, 4 H), 1.46-1.37 (m, 4 H), 1.25-1.20 (2 H), 0.79 (t, 3 H). LC-MS *m/z* 471.33 (MH^+), retention time 2.88 min (method 2).

Example 15

Preparation of *N*-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide



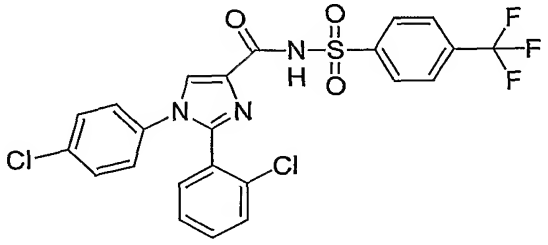
Step 1. 2-(2-Chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (1.5 g, 4.5 mmol) was dissolved in dichloromethane (40 mL). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 946 mg, 4.95 mmol) and triethylamine (500 mg, 4.95 mmol) were added followed by pentafluorophenol (815 mg, 4.37 mmol). The mixture was stirred at rt under argon for one hour before it was washed with 5% HCl, sodium bicarbonate solution, and then brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the crude product (1.26 g) which was chromatographed over silica gel (20% EtOAc in hexanes) to afford pentafluorophenyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (0.73 g, 32% yield): LC-MS *m/z* 499.0 (MH^+), retention time 3.93 min (method 1).

Step 2. The pentafluorophenol ester (60 mg, 0.12 mmol) and exo-norbornylamine (40 mg, 0.36 mmol) were dissolved in dichloromethane (2 mL), treated with triethylamine (49 mg, 0.48 mmol), and stirred at rt overnight. The mixture was then washed with 5% aqueous HCl, sodium

bicarbonate solution and brine, dried ($MgSO_4$), filtered, and concentrated. Pure *N*-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide was thus obtained (30 mg, 59% yield): LC-MS *m/z* 426.1 (MH^+), retention time 3.49 min (method 1).

Example 16

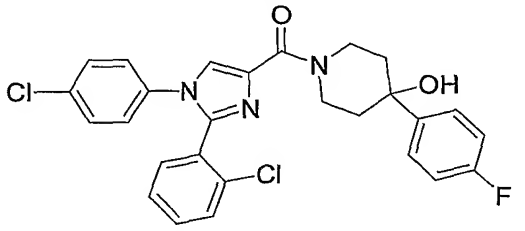
Preparation of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(trifluoromethyl) benzenesulfonamide



In a 20-mL screw-cap vial, 250 mg (0.75 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid, 18.3 mg DMAP (0.15 mmol), 1.25 g PS-Carbodiimide (1.5 mmol) (polystyrene-supported cyclohexylcarbodiimide ,Argonaut Technologies Inc., San Carlos, CA), 169 mg α,α,α-trifluoro-p-toluenesulfonamide (0.75 mmol), and 12 mL dichloromethane were added, and the reaction mixture was mixed by orbital shaking at rt overnight. The reaction mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 2 mL MeOH and purified by preparative HPLC to give 39.3 mg of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(trifluoromethyl)benzenesulfonamide (beige solid, 10% yield). ^1H NMR (400 MHz, CD3COCD3) δ 8.25 (d, 2 H), 7.85 (s, 1 H), 7.75 (s, 2H), 7.20-7.40 (m, 6 H), 6.95 (t, 2 H); LC-MS *m/z* 540 (MH^+), retention time 3.36 min (method 2).

Example 17

Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol

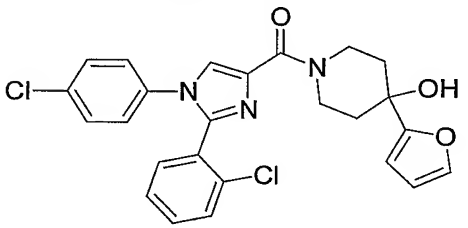


A solution of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone (0.1 g, 0.24 mmol, prepared as described in Example **13**) in THF (4 mL) was added

dropwise to a solution of 4-fluorophenylmagnesium bromide (0.6 mL, 0.60 mL) at –78°C. The mixture was stirred at –78°C for 2 h then allowed to warm up to 30°C. Saturated NH_4Cl (3 mL) was added slowly followed by water (3 mL). The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over $MgSO_4$. The product (0.056 g, 46 %) was isolated by column (50 % ethyl acetate in hexane). MS (Electrospray) 510.1 $(M)^+$; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.81 (s, 1H), 7.50-7.24 (m, 8H), 7.10-6.98 (m, 4H), 5.33-5.17 (m, 1H), 4.74-4.57 (m, 1H), 3.68 (t, 1H), 3.31 (t, 1H), 2.15 (br, 2H), 1.83 (d, 2H).

Example18

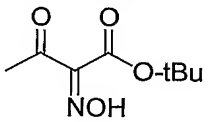
Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(2-furyl)-4-piperidinol



BuLi (0.875 mL, 1.40 mmol, 1 M solution in THF) was added slowly to a solution of furan (0.106 mL, 1.45 mmol) in THF (2 mL) at –78°C, and the mixture was stirred at –78°C for 1 h. A solution of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone (0.3 g, 0.68 mmol) in THF (1 mL) was added slowly. The mixture was stirred at -78°C for 2 h and saturated NH_4Cl (3 mL) and water added. The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over $MgSO_4$. The product (0.142 g, 61 %) was isolated by column (ethyl acetate). MS (Electrospray) 482 $(M)^+$; ^1H NMR (300 MHz, CD_2Cl_2) δ.7.85 (s, 1H), 7.51-7.31 (m, 7H), 7.10-6.98 (m, 4H), 7.17-7.10 (m, 2H), 6.39 (s, 1H), 6.29 (s, 1H), 4.68 (br, 1H), 4.28 (br, 1H), 3.94 (br, 1H), 3.57 (br, 1H), 2.26-1.91 (m, 4H).

Example 19

Preparation of *t*-butyl 2-hydroxyimino-3-oxobutanoate

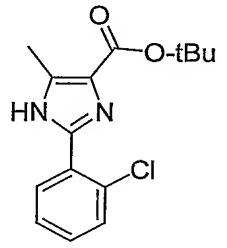


t-Butyl acetoacetate (5.0 g, 31.6 mmol) was dissolved in acetic acid (4.5 mL), cooled by an ice water bath, and treated with sodium nitrite (2.45 g, 35.5 mmol) in water (5.5 mL) while the internal temperature was kept at <10°C (*see, e.g.,* U.S. Patent No. 4,743,586). After the addition

was complete, the mixture was stirred at rt for 30 minutes before water (16 mL) was added. After 2 h, extraction with ether (3 x 25 mL), which was washed with water (10 mL), sodium bicarbonate solution (3 x 10 mL), and water (20 mL), gave *t*-butyl 2-hydroxyimino-3-oxobutanoate as a white solid (5.52 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 2.39 (s, 3H), 1.58 (s, 9H).

Example 20

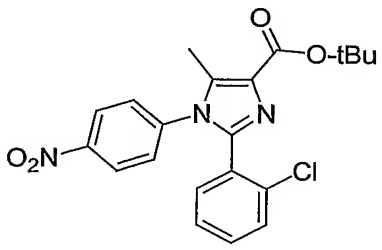
Preparation of *t*-Butyl 2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate



t-Butyl 2-hydroxyimino-3-oxobutanoate (0.50 g, 2.67 mmol) was mixed with 2-chlorobenzylamine (0.34 mL, 2.82 mmol) in anhydrous acetonitrile (10 mL), and heated at reflux for 3 h. Upon cooling, the suspension was filtered, and the filtered material was washed with a small amount of acetonitrile to afford a white solid (0.379 g). The filtrate was concentrated and the residue chromatographed over silica gel (25% EtOAc in hexane) to give *t*-butyl 2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate as a yellow foam (0.262 g, 82% combined yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (br, 1H), 8.29 (m, 1H), 7.38 (m, 3H), 2.52 (s, 3H), 1.60 (s, 9H).

Example 21

Preparation of *t*-Butyl 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate

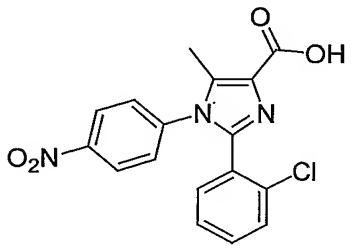


t-Butyl 2-(2-chlorophenyl)-5-methylimidazole-4-carboxylate (70 mg, 0.24 mmol) was mixed with 4-fluoro-1-nitrobenzene (27 μL, 0.25 mmol) and potassium carbonate (66 mg, 0.48 mmol) in dry DMF and heated at 120°C for 4 h. The mixture was diluted with water and filtered to give a yellow solid which was chromatographed over silica gel (40% EtOAc in hexane) to afford a

yellow solid (72 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$)δ 8.20 (m, 2H), 7.51 (m, 1H), 7.25 (m, 5H), 2.45 (s, 3H), 1.66 (s, 9H).

Example 22

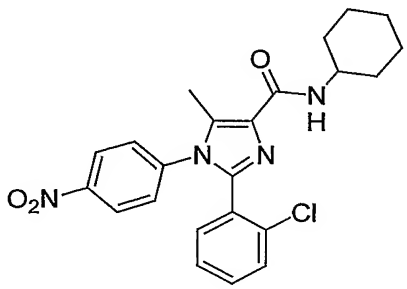
Preparation of 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylic acid



t-Butyl 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate (69 mg, 0.17 mmol) was dissolved in dry dichloromethane (2 mL) and treated dropwise with trifluoroacetic acid (2 mL). After stirring at rt for 2 h, the solution was concentrated to give 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylic acid as a yellow foam, which was used without purification in the preparation of Example **23**.

Example 23

Preparation of *N*-cyclohexyl-2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxamide

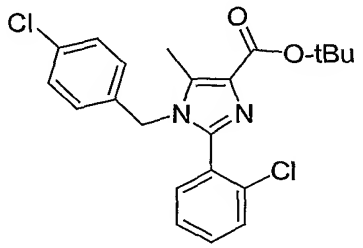


The carboxylic acid obtained from Example **22** was dissolved in dry dichloromethane (3 mL), cooled by an ice water bath, and treated with 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (39 mg, 0.20 mmol) and dimethylaminopyridine (46 mg, 0.38 mmol). The mixture was stirred at rt for 1 h before cyclohexylamine (23 μL, 0.20 mmol) was added. The solution was stirred overnight, diluted with dichloromethane, washed with water and ammonium chloride solution, dried (sodium sulfate), and filtered. The filtrate was concentrated to afford a yellow oil (70 mg) which was chromatographed over silica gel (35% EtOAc in hexane) to

give *N*-cyclohexyl-2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxamide as a yellow solid (50 mg, 67%): mp 217-220°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2H), 7.41 (m, 1H), 7.25 (m, 5H), 7.12 (m, 1H), 3.95 (m, 1H), 2.55 (s, 3H), 2.00 (m, 2H), 1.75 (m, 2H), 1.61 (m, 1H), 1.30 (m, 5H); LC-MS *m/z* 439.2 (MH^+), retention time 3.41 min (method 1).

Example 24

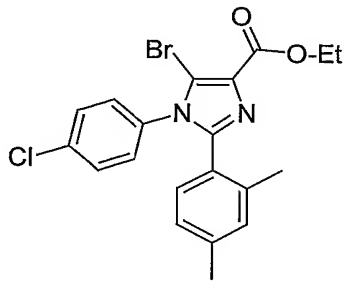
Preparation of tert-butyl 1-(4-chlorobenzyl)-2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate



t-Butyl 2-(2-chlorophenyl)-5-methylimidazole-4-carboxylate (70 mg, 0.24 mmol) was mixed with 4-chlorobenzyl bromide (50 mg, 0.24 mmol) and potassium carbonate (66 mg, 0.48 mmol) in dry acetonitrile (3 mL) and heated at reflux overnight. The next day, additional 4-chlorobenzyl bromide (10 mg, 0.05 mmol) was added, and the reaction mixture was again heated at reflux overnight. The next day, water was added to the cooled mixture, which was subsequently extracted with EtOAc. The extract was washed with aqueous NaCl, dried ($NaSO_4$), filtered, and concentrated to give a colorless oil (113 mg). It was chromatographed over silica gel (25% EtOAc in hexane) to afford tert-butyl 1-(4-chlorobenzyl)-2-(2-chlorophenyl)-5-methyl-1H-imidazole-4-carboxylate as a white foam (61 mg, 61% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.17 (d, 2H), 6.78 (d, 2H), 5.33 (br, 2H), 2.55 (s, 3H), 1.50 (s, 9H); LC-MS *m/z* 417.1 (MH^+), retention time 3.23 min (method 1).

Example 25

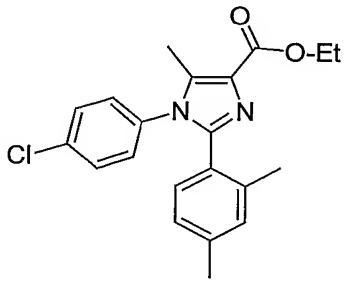
Preparation of ethyl 5-bromo-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate



Ethyl 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate (1.23 g, 3.47 mmol) was dissolved in EtOH (15 mL) and treated with *N*-bromosuccinimide (1.25 g, 7.02 mmol). The solution was stirred at rt for 3 h. Water was added. Extraction with dichloromethane, which was then washed with NaCl solution, gave an orange solid (1.94 g). Purification by chromatography over silica gel (20% EtOAc in hexane) afforded a light tan solid (1.028 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H), 7.03 (d, 2H), 7.00 (m, 1H), 6.86 (m, 2H), 4.44 (q, 2H), 2.26 (s, 3H), 2.10 (s, 3H), 1.43 (t, 3H); LC-MS *m/z* 433.1 (MH^+), retention time 3.84 min (method 1).

Example 26

Preparation of ethyl 1-(4-chlorophenyl)-5-methyl-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate

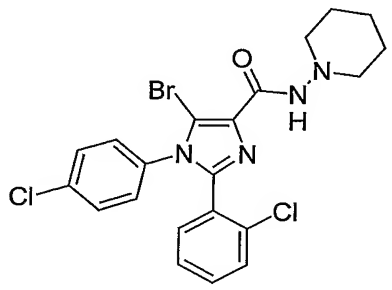


Ethyl 5-bromo-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate (430 mg, 0.99 mmol) was dissolved in dry DMF (5 mL) in a pressure tube and treated with tetramethyltin (1.3 mL, 9.38 mmol), palladium acetate (9 mg, 0.04 mmol), and tri-(*o*-tolyl)phosphine (26 mg, 0.085 mmol). The mixture was heated at 110°C for 15 minutes. After the

mixture was cooled to rt, water was added (25 mL). The mixture was extracted with dichloromethane (2 x 25 mL), and the organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated, to give a light brown oil (436 mg). Purification by chromatography over silica gel (33% EtOAc in hexane) afforded ethyl 1-(4-chlorophenyl)-5-methyl-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate as a white foam (338 mg, 93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, 2H), 7.00 (m, 3H), 6.85 (m, 2H), 4.41 (q, 2H), 2.42 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H), 1.41 (t, 3H).

Example 27

Preparation of 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide

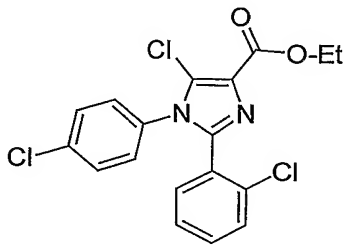


Step 1. A solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (50 mg, 0.15 mmol) and *N*-bromosuccinimide (88 mg, 0.49 mmol) in dimethylformamide (5 mL) was stirred at 75°C for 3 days. The solution was purified by preparative HPLC to give 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid as a white solid (30.7 mg, 50%). LC-MS *m/z* 411.2 (MH^+), retention time 2.70 min (method 2).

Step 2. As described previously for Example **14**, 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid was converted to 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide. LC-MS *m/z* 493.0 (MH^+), retention time 2.63 min (method 2). ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.29 (m, 6H, Ph), 7.05 (m, 2H, Ph), 3.68 (m, 3H, piperidine), 3.36 (m, 2H, piperidine), 1.88 (m, 3H, piperidine), 1.57 (m, 2H, piperidine).

Example 28

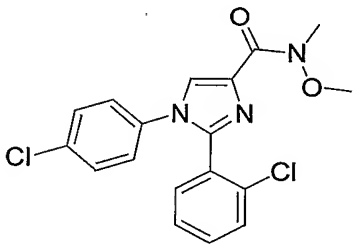
Ethyl 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate



To a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (270 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) was added SO_2Cl_2 (1.6 mL, 20 mmol). The mixture was heated at reflux overnight, and diluted with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (33% EtOAc in hexane) to give ethyl 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (60 mg) in 20% yield as a white solid: LC-MS *m/z* 395.0 (MH^+), retention time 3.45 min (method 1). This intermediate, which is an example of Formula X in Scheme 2, was converted into 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Table entry 21).

Example 29

Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide

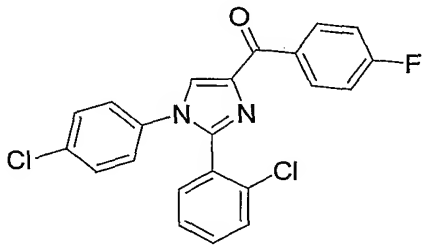


A solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride (4.71 g, 13.4 mmol, prepared by the method described in Example **13**, step 1) in 10 mL dichloromethane was added to a solution of *N, O*-dimethylhydroxyamine hydrochloride (1.44 g, 14.7 mmol) and triethylamine (5.6 mL, 40.2 mmol) in 60 mL dichloromethane in an ice water bath under argon with stirring. The bath was removed upon completion of addition. Stirring was

continued for 1 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated down under reduced pressure. The crude product was purified on silica gel, eluting with ethyl acetate to yield 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide as an off-white solid (4.20 g, 83%): R_f = 0.22 (ethyl acetate).

Example 30

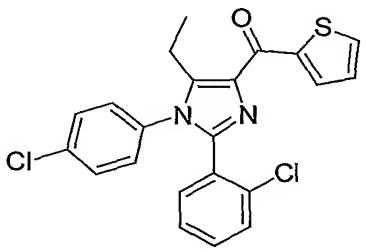
Preparation of [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl](4-fluorophenyl)-methanone



To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-methoxy-*N*-methyl-1*H*-imidazole-4-carboxamide (50.0 mg, 0.133 mmol) in 1.5 mL THF was added a 1.0 M solution of 4-fluorophenylmagnesium bromide (0.27 mL, 0.27 mmol) under argon at rt with stirring. The resultant mixture was stirred for 30 minutes and a saturated aqueous solution of NH_4Cl was added. The mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated down *in vacuo*. The crude product was purified on HPLC to give [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl](4-fluorophenyl)-methanone as a solid (38.0 mg, 69%): R_f = 0.58 (1:1 ethyl acetate / hexanes).

Example 31

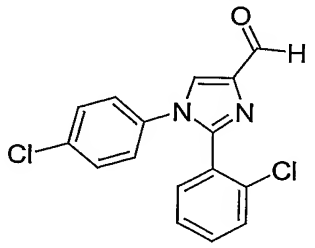
Preparation of [2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazol-4-yl](2-thienyl)-methanone



To a solution of 2-bromothiophene (0.22 g, 1.36 mmol) in 2 mL THF was added 0.84 mL of a 1.6 M solution of BuLi in hexane under argon at –78°C with stirring. The stirring was continued for 1 h. To this was added a solution of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone in 2 mL THF. The resultant mixture was stirred and gradually allowed to warm up to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate. The organic layer was concentrated and the crude product was purified by HPLC to yield [2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazol-4-yl](2-thienyl)-methanone as a solid (60 mg, 31%): $R_f = 0.13$ (1:5 ethyl acetate / hexanes).

Example 32

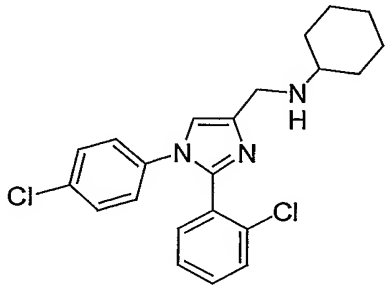
Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxaldehyde



To a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (200 mg, 0.51 mmol) in toluene (10 mL) at –78°C was added DIBAH (2.0 mL) in toluene dropwise. The resulting solution was stirred at rt, quenched with 1N HCl (0.5 mL). The organic layer was washed with 1N HCl (5 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (50% EtOAc in hexane) to give the product (62 mg, 38% yield). LC-MS *m/z* 317.0 (MH^+), retention time: 2.75 min (method 1).

Example 33

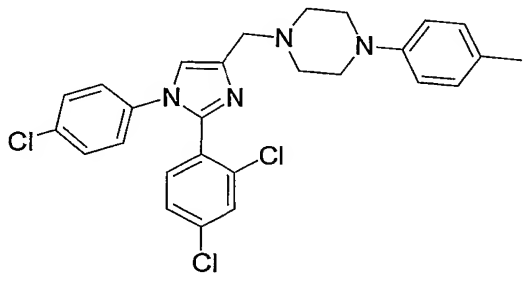
Preparation of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]methyl}-*N*-cyclohexylamine



To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxaldehyde (62 mg, 0.20 mmol) in methanol (7 mL) was added cyclohexylamine (58 μL, 0.5 mmol). The mixture was stirred overnight, and cooled to 4°C. $NaBH_4$ (40 mg, 1.1 mmol) was added. The mixture was stirred at rt for 1 h, and concentrated. The residue was dissolved in CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative TLC (50% EtOAc in hexane) to give N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]methyl}-*N*-cyclohexylamine (65 mg, 81% yield): LC-MS *m/z* (400.7 MH^+), retention time 2.32 min (method 1).

Example 34

Preparation of 1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazol-4-yl]methyl}-4-(4-methylphenyl)piperazine



To a suspension of lithium aluminum hydride (21 mg, 0.54 mmol) in THF (2 mL), 1-(4-methylphenyl)piperazine hydrochloride (32 mg, 0.13 mmol) was added. After 10 minutes, a solution of ethyl 2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (39 mg,

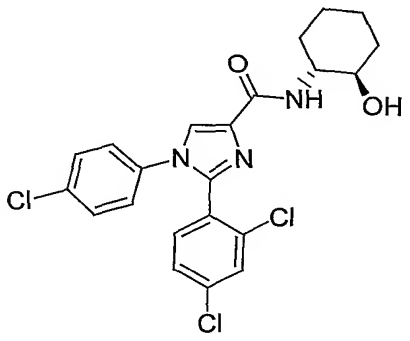
0.1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 10 minutes, and diluted by water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by HPLC (YMC-packed Pro C18 20 x 150 mm column, 10-90% CH_3CN in H_2O/TFA, 25 mL/min) to give the product 1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazol-4-yl]methyl}-4-(4-methylphenyl)-piperazine (1.4 mg, 2% yield): LC-MS *m/z* 511.1 (MH^+), retention time 2.94 min (method 1). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.29 (3H, s), 3.42-3.49 (8H, br), 4.39 (2H, s), 6.85- 7.41 (11H, m), 7.54 (1H, s).

Other Procedures

In certain cases, the products and intermediates prepared by the experimental methods described in Examples **1-34** were converted into additional products, by applying the appropriate additional chemical steps. These additional examples are described below.

Example 35

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1R,2R)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide

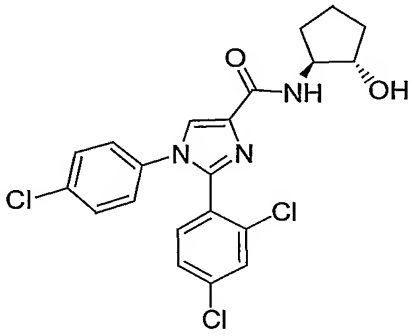


To a solution of *N*-[(1R, 2R)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 278, prepared according to the procedures described in Examples **13** and **14**) (100 mg, 0.18 mmol) in CH_2Cl_2 (2 mL), TMSI (iodotrimethylsilane) (60 μL, 0.42 mmol) was added. The mixture was stirred at rt overnight, and diluted with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1R,2R)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide (56 mg, 67% yield) as a yellow solid: LC-MS *m/z* 464.3 (MH^+), retention time 3.19 min (method 1); Rf = 0.67

(EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16-1.30 (4H, m), 1.66-1.69 (2H, m), 1.98-2.02 (2H, m), 3.37-3.39 (1H, m), 3.70-3.80 (1H, m), 3.99-4.06 (1H, m), 6.96- 7.37 (8H, m), 7.78 (1H, s).

Example 36

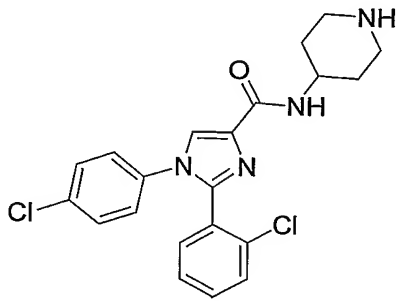
1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1S, 2S)-2-hydroxycyclopentyl]-1*H*-imidazole-4-carboxamide



To a solution of *N*-[(1S, 2S)-2-(benzyloxy)cyclopentyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 282, prepared according to the procedures described in Examples **13** and **14**) (119 mg, 0.22 mmol) in CH_2Cl_2 (4 mL), TMSI (0.2 mL, 1.4 mmol) was added. The mixture was stirred at rt overnight, and diluted by water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1S, 2S)-2-hydroxycyclopentyl]-1*H*-imidazole-4-carboxamide (80 mg, 82% yield) as a white foam: LC-MS *m/z* 450.0 (MH^+), retention time 3.24 min (method 1); Rf = 0.45 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-2.24 (6H, m), 3.97-4.15 (2H, m), 7.03-7.42 (7H, m), 7.86 (1H, s).

Example 37

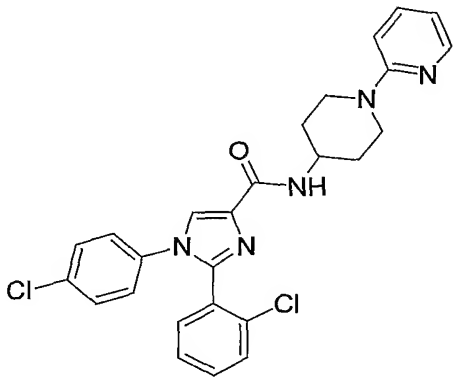
2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(4-piperidinyl)-1*H*-imidazole-4-carboxamide



To a solution of ethyl 4-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}amino)-1-piperidinecarboxylate (Table entry 221) (0.595 g, 1.221 mmol) in CH_2Cl_2 (10 mL) was added TMSI (0.176 mL, 2.7 mmol). The mixture was heated at reflux for 3 h, diluted by methanol, and concentrated. The residue was dissolved in methanol and NaOMe (0.62 mmol) was added. The mixture was concentrated and purified by flash chromatography (2M NH_3 in methanol : EtOAc = 15: 85) to afford the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-piperidinyl)-1*H*-imidazole-4-carboxamide (180 mg, 36% yield): LC-MS *m/z* 415.3 (MH^+), retention time 2.22 min (method 1); Rf = 0.25 (1:1 EtOAc/2M NH_3 in MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.51 (2H, m), 1.91-2.15 (3H, br), 2.63-2.78 (2H, m), 3.03-3.09 (2H, m), 3.97-4.15 (1H, m), 6.96-7.52 (8H, m), 7.81 (1H, s).

Example 38

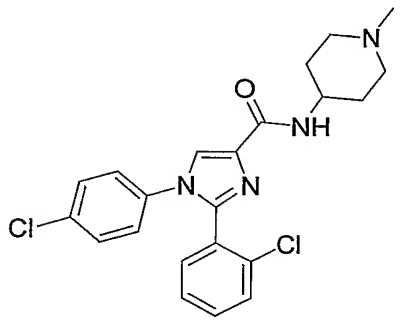
2-(2-Chlorophenyl)-1-(4-chlorophenyl)-*N*-[1-(2-pyridinyl)-4-piperidinyl]-1*H*-imidazole-4-carboxamide



A flask was charged with 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(4-piperidinyl)-1*H*-imidazole-4-carboxamide (Example **37**) (100 mg, 0.24 mmol), 2-bromopyridine (0.55 mg, 0.22 mmol), $Pd_2(dba)_3$ (38 mg, 0.24 mmol), BINAP (1.18 mg, 0.0019 mmol), NaO*t*Bu (33.6 mg, 0.35 mmol), and toluene (2 mL). The reaction mixture was heated at reflux overnight, cooled to rt, and diluted with CH_2Cl_2. The solid was filtered off. The solvent was evaporated. The residue was purified by flash chromatography (33% EtOAc in hexane) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[1-(2-pyridinyl)-4-piperidinyl]-1*H*-imidazole-4-carboxamide (55 mg, 47% yield): LC-MS *m/z* 492.1 (MH^+), retention time 2.47 min (method 1); Rf = 0.33 (50% EtOAc in hexane).

Example 39

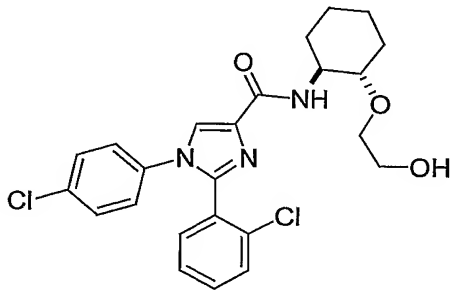
2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-methyl-4-piperidinyl)-1*H*-imidazole-4-carboxamide



To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(4-piperidinyl)-1*H*-imidazole-4-carboxamide (Example **37**) (80 mg, 0.2 mmol) in CH_2Cl_2 (6 mL) was added CH_3I (28.4 mg, 0.2 mmol) and Et_3N (0.031 mL, 0.22 mmol). The reaction mixture was heated at reflux for 5 h, cooled to rt, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (2M NH_3 in methanol : EtOAc = 1:10) to afford the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-methyl-4-piperidinyl)-1*H*-imidazole-4-carboxamide (24 mg, 28% yield): LC-MS *m/z* 429.1 (MH^+), retention time 2.27 min (method 1); Rf = 0.31 (EtOAc: 2M NH_3 in MeOH = 9:1).

Example 40

2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[trans-2-(2-hydroxyethoxy)cyclohexyl]-1*H*-imidazole-4-carboxamide

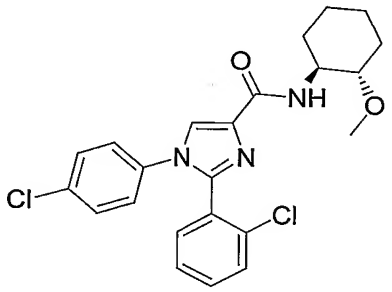


To a solution of 2-{[trans-2-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}amino)cyclohexyl]oxy}-ethyl acetate (Table entry 286) (31 mg, 0.06 mmol) in THF (7 mL) and water (0.7 mL) was added $NaBH_4$ (5 mg, 0.13 mmol) portionwise over 1 h with the

temperature kept below 20°C. The mixture was stirred at rt overnight, cooled to 5°C, treated with acetone (1 mL), and then concentrated. The residue was dissolved in CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (2.5% methanol in EtOAc) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1R, 2S)-2-(2-hydroxyethoxy)cyclohexyl]-1*H*-imidazole-4-carboxamide (7.5 mg, 26% yield): LC-MS *m/z* (474.8 MH^+), retention time 2.91 min (method 1); Rf = 0.17 (EtOAc).

Example 41

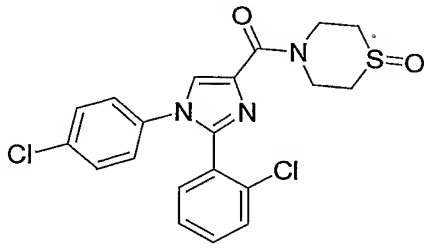
2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[trans-2-methoxycyclohexyl]-1*H*-imidazole-4-carboxamide



A flask was charged with 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[trans-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide (Table entry 336) (35 mg, 0.1 mmol), benzene (3 mL), 50% aqueous NaOH (2.5 mL), and Bu_4NHSO_4 (17 mg). While the mixture was stirred vigorously at 10°C, CH_3I (19 µL, 0.3 mmol) was added dropwise rapidly. The mixture was stirred for another 30 minutes, and diluted with water (5 mL) and hexane (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (75% EtOAc in hexane) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1R,2S)-2-methoxycyclohexyl]-1*H*-imidazole-4-carboxamide (23 mg, 63% yield): LC-MS *m/z* 444.2 (MH^+), retention time 3.24 min (method 1).

Example 42

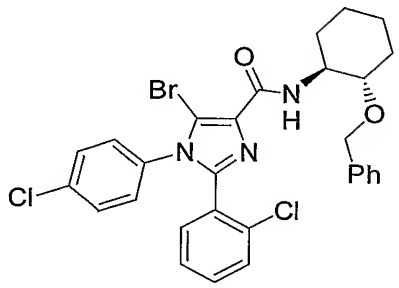
4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}thiomorpholine 1-oxide



To a solution of 4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl} thiomorpholine (Table entry 176) (30 mg, 0.072 mmol) in acetone (2 mL), was added 30% aqueous H_2O_2 (0.09 mmol). The resulting solution was stirred at rt for 36 h, diluted with water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (20% MeOH in EtOAc) to give the product 4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}thiomorpholine 1-oxide (17 mg, 54% yield): LC-MS *m/z* 434.5 (MH^+), retention time 2.55 min (method 1); Rf = 0.47 (17% EtOAc in hexane).

Example 43

N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide

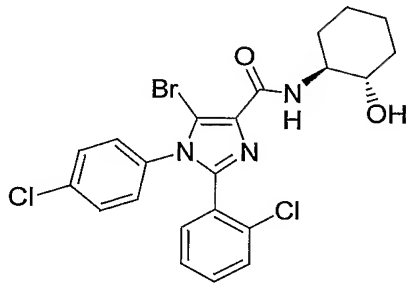


A solution of *N*-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 276) (198 mg, 0.380 mmol) and *N*-bromosuccinimide (88 mg, 0.49 mmol) in dimethylformamide (5 mL) was stirred at 75°C for 3 days. The solution was purified by preparative HPLC to give *N*-[(1S,2S)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-

carboxamide as a white solid (196 mg, 86%). LC-MS *m/z* 598.1 (MH^+), retention time 3.72 min (method 2).

Example 44

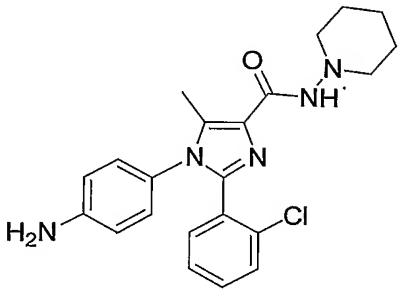
5-Bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1S,2S)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide



As described previously for Example **35**, *N*-[(1S,2S)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide (Example **43**) was de-benzylated by treatment with iodotrimethylsilane to give 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1S,2S)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide. LC-MS *m/z* 508.1 (MH^+), retention time 2.96 min (method 2). ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.43 (d, 1H, Ph), 7.27 (m, 5H, Ph), 7.06 (m, 2H, Ph), 3.70 (m, 1H, CHOH), 3.44 (m, 1H, CHN), 1.95 (m, 2H, cyclohexane), 1.64 (m, 2H, cyclohexane), 1.24 (m, 4H, cyclohexane).

Example 45

1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide

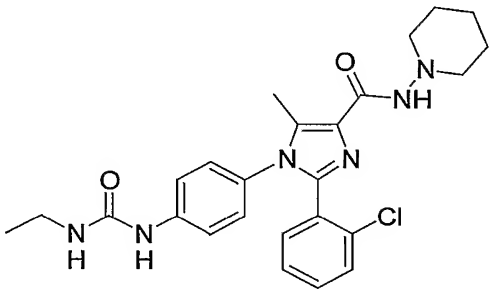


A sample of 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Table entry 41) (111 mg, 0.25 mmol) was added as a suspension in ethanol (5 mL) to Degussa-type palladium on carbon (10% by weight, 12 mg). The mixture was

hydrogenated at atmospheric pressure and rt for 2 h. Filtration of the mixture through Celite and concentration of the filtrate gave 1-(4-aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide as a yellow foam (104 mg, 100%). This material was used without purification for the preparation of compounds of the invention, such as Example **46**.

Example 46

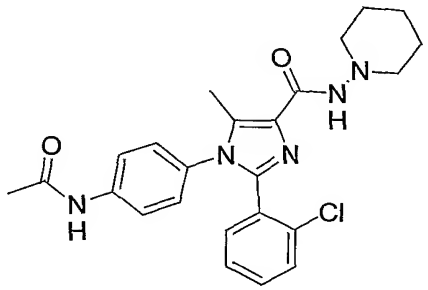
2-(2-chlorophenyl)-1-(4-{[(ethylamino)carbonyl]amino}phenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide trifluoroacetate



1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Example **45**) (52 mg, 0.13 mmol) was dissolved in dry dichloromethane (2 mL) and added to ethyl isocyanate (20 μL, 0.25 mmol). The solution was stirred at rt for 6 h before more ethyl isocyanate (30 μL, 0.38 mmol) was added. After stirring overnight, the mixture was heated at reflux for 1 h. The solvent was evaporated to give a yellow solid which was chromatographed over silica gel (3% MeOH in EtOAc) to afford semi-pure product (21 mg). This material was further purified by HPLC (YMC-packed Pro C18 15 x 200 mm column, 30-90% CH_3CN in H_2O/TFA, 20 mL/min.) to give 2-(2-chlorophenyl)-1-(4-{[(ethylamino)carbonyl]amino}phenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide trifluoroacetate as a white solid (12 mg, 13% yield): LC-MS *m/z* 481.4 (MH^+), retention time 2.35 min (method 1).

Example 47

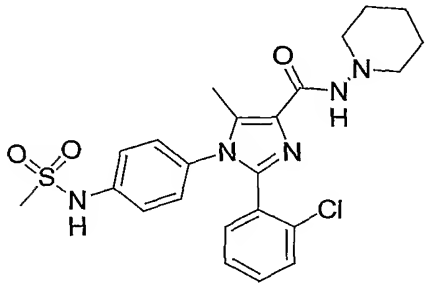
1-[4-(acetylamino)phenyl]-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide



1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Example **45**) (51 mg, 0.12 mmol) was dissolved in dry dichloromethane (2 mL) and treated with acetic anhydride (14 μL, 0.15 mmol) dropwise. The solution was stirred at rt for 4 h, and then the solvent was evaporated to give an amber oil. It was purified by HPLC (YMC-packed Pro C18 15 x 200 mm column, 30-90% CH_3CN in H_2O/TFA, 20 mL/min.) to afford an off-white solid (13 mg, 15%): LC-MS *m/z* 452.3 (MH^+), retention time 2.31 min (method 1).

Example 48

2-(2-Chlorophenyl)-5-methyl-1-{4-[(methylsulfonyl)amino]phenyl}-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide trifluoroacetate

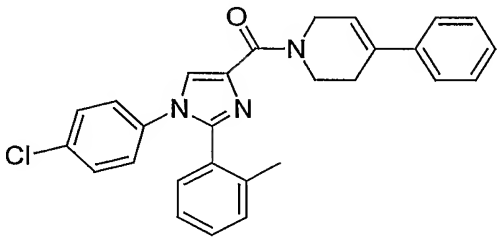


1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Example **45**) (52 mg, 0.13 mmol) was dissolved in dry dichloromethane (2 mL), cooled by an ice water bath, and the mixture was then treated with methanesulfonyl chloride (12 μL, 0.16 mmol) and triethylamine (21 μL, 0.15 mmoL). The solution was stirred at rt overnight, and then the solvent was evaporated. The residue was purified by HPLC (YMC-packed Pro C18

15 x 200 mm column, 30-90% CH_3CN in H_2O/TFA, 20 mL/min.) to afford a light tan solid (21 mg, 27%): LC-MS *m/z* 488.4 (MH^+), retention time 2.29 min (method 1).

Example 49

1-{[1-(4-Chlorophenyl)-2-(2-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine



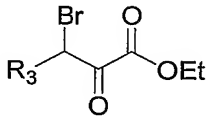
A 30-mg sample of 1-{[2-(2-methylphenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol (Table entry 414), was dissolved in 20 mL dichloromethane, and then 5 mL 2M HCl in ether was added to the solution. Evaporation of the solvent at high temperature (ca. 70°C, 16 hr) in a multiple sample evaporator (GeneVac) gave 1-{[1-(4-chlorophenyl)-2-(2-methylphenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine (yellow solid). ^1H NMR (400 MHz, CD_3COCD_3) δ 8.31 (s, 1H), 7.05-7.35 (m, 13 H), 6.05 (s, 1 H), 4.2 (m, 2 H), 3.85 (m, 2H), 2.5 (m, 2H), 2.0 (s, 3H); LC-MS *m/z* 454 (MH^+), retention time 2.92 min (method 2).

Preparation of Intermediates

Experimental procedures for the preparation of chemical reagents that are not commercially available are described below.

Intermediate A

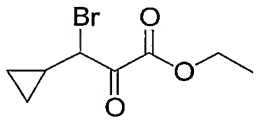
Ethyl 3-bromo-2-oxobutanoate



This bromo pyruvate was prepared by oxidative bromination of the corresponding hydroxyesters, by the procedure described by Plouvier et al., (Heterocycles 32:693-701, 1991). In a similar manner, ethyl 3-bromo-2-oxopentanoate and ethyl 3-bromo-2-oxohexanoate were prepared.

Intermediate B

Ethyl 3-bromo-3-cyclopropyl-2-oxopropanoate



The procedure was similar to that reported in the literature (*see, e.g.*, J. Org. Chem. 37, 505-506, 1972).

Step 1. To a solution of $BF_3.Et_2O$ (57.5 mL, 0.454 mmol) in $CHCl_3$ (180 mL) heated at reflux was added dropwise, over a 1-h period, a solution of 1,3-propanedithiol (22.7 mL, 0.227 mmol), followed by ethyl diethoxyacetate (40 g, 0.227 mmol) in $CHCl_3$ (40 mL). The resulting mixture was heated for 30 minutes, and then cooled to rt. The cooled solution was washed 2 times with water, once with saturated aqueous $NaHCO_3$, and then re-washed with water. The combined organic phases were dried over $MgSO_4$, then evaporated to give 41 g (94%) of ethyl 1,3-dithiane-2-carboxylate as a yellow oil, which was used in the next step without purification. ^1H NMR ($CDCl_3$): δ 4.24 (2H, q, J = 7.2 Hz), 4.17 (1H, s), 3.46-3.39 (2H, m), 2.64-2.58 (2H, m), 2.18-2.01 (2H, m), 1.30 (3H, t, J = 7.2 Hz).

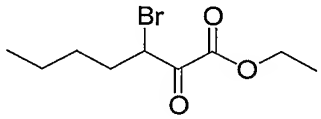
Step 2. To a suspension of NaH (95 %, 2.8 g, 111 mmol) in dry toluene (120 mL) stirring at 0°C was dropwise added, over 10 minutes, a solution of bromomethylcyclopropane (15 g, 111 mmol), and ethyl 1,3-dithiane-2-carboxylate (17.77 g, 92.58 mmol) in dry DMF (40 mL). The ice bath was removed and the solution was stirred overnight at rt. Water was added to the solution and the phases were separated. The organic phase was dried over $MgSO_4$, then evaporated to give 19.6 g (50%) of ethyl 2-(cyclopropylmethyl)-1,3-dithiane-2-carboxylate, which was used in the next step without purification. ^1H NMR ($CDCl_3$): δ 4.26 (2H, q, J = 7.2 Hz), 3.30-3.23 (2H, m), 2.69-2.64 (2H, m), 2.16-2.11 (1H, m), 1.96 (2H, d, J = 6.8 Hz), 1.91-1.81 (1H, m), 1.34 (3H, t, J = 7.2 Hz), 0.93-0.86 (1H, m), 0.52-0.47 (2H, m), 0.20-0.16 (2H, m).

Step 3. A solution of ethyl 2-(cyclopropylmethyl)-1,3-dithiane-2-carboxylate (19.6 g, 79.67 mmol) in CH_3CN (20 mL) was slowly added, over 30 minutes, to a well-stirred suspension of NBS (N-bromosuccinimide) in CH_3CN (210 mL) and water (55 mL). After the mixture was stirred for 1 h, the resulting red solution was poured into an ice-cold CH_2Cl_2-Hexane solution (1:1 500 mL). The resulting mixture was washed with saturated aqueous $NaHSO_3$ and water. The colorless organic phase was carefully washed with saturated aqueous K_2CO_3 and water. The organic phase was dried over $MgSO_4$, then evaporated to give 6.88 g (55%) of ethyl 3-cyclopropyl-2-oxopropanoate as a yellow oil. ^1H NMR ($CDCl_3$): δ 4.29 (2H, q, J = 8 Hz), 2.71 (2H, d, J = 9 Hz), 1.35 (3H, t, J = 8 Hz), 1.05-0.98 (1H, m), 0.59-0.54 (2H, m), 0.17-0.14 (2H, m).

Step 4. To a solution of ethyl 3-cyclopropyl-2-oxopropanoate (4.75g, 30.44 mmol) in CCl_4 (60 mL) at rt was added NBS (5.96 g 33.49 mmol). The resulting mixture was heated at reflux overnight, then cooled, filtered, and evaporated to provide ethyl 3-bromo-3-cyclopropyl-2-oxopropanoate; ^{1}H NMR ($CDCl_3$): δ 4.46-4.32 (3H, m), 1.41 (3H, t, J = 8 Hz), 0.96-0.86 (1H, m), 0.55-0.50 (2H, m), 0.07-0.03 (2H, m). This compound was used without purification for the preparation of compounds of the invention such as 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-cyclopropyl-1H-imidazole-4-carboxamide hydrochloride (Table entry 22). In a similar manner, ethyl 3-bromo-3-cyclobutyl-2-oxopropanoate and ethyl 3-bromo-3-isobutyl-2-oxopropanoate were prepared.

Intermediate C

Ethyl 3-bromo-2-oxoheptanoate

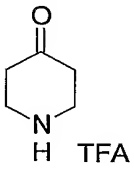


Step 1. To a suspension of LiI (23.61 g, 176.44 mmol) in THF (200 mL) at rt was slowly added Cu_2Br_2 (25.30 g, 88.22 mmol). A vigorous exothermic reaction occurred, and the mixture was then cooled to –78°C. Pentylmagnesium bromide (2M, 36.76 mL, 88.22 mmol) was slowly added at –78°C, and followed soon after by ethyl chloro(oxo)acetate (10g, 73.52 mmol). The resulting solution was stirred 10 minutes at –78°C, then quenched by dropwise addition of water. The mixture was allowed to warm to rt, and then the organic phase was separated, dried (MgSO4), and evaporated. Purification by flash chromatography using 9:1 hexane/EtOAc as eluant gave ethyl 2-oxoheptanoate as a colorless oil (3.0 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33-4.21 (m, 2 H), 2.82 (m, 2 H), 1.63-1.59 (m, 2 H), 1.63-11.19 (m, p H), 0.9-0.83 (m, 3 H). LC-MS *m/z* 279.21 (MH^+), retention time 2.42 min (method 2).

Step 2. To a cold solution of ethyl 2-oxoheptanoate (2 g, 11.62 mmol) in AcOH (20 mL), was added Br_2 (596 µL, 11.62 mmol). The mixture was stirred 20 minutes at 0°C, then the mixture was allowed to warm to rt. After the mixture was stirred for 3 h, water and CH_2Cl_2 were added. The organic phase was separated, dried ($MgSO_4$), and evaporated to give crude ethyl 3-bromo-2-oxoheptanoate as a dark oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05-5.01 (m, 1 H), 4.45-4.20 (m, 2 H), 2.18-1.94 (m, 2 H), 1.74-1.57 (m, 2 H), 1.48-1.17 (m, 5 H), 0.95-0.82 (m, 3 H). This compound was used without purification for the preparation of compounds of the invention such as 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide hydrochloride (Table entry 20).

Intermediate D

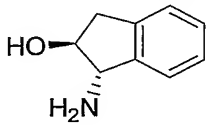
4-Piperidinone trifluoroacetate



A suspension of t-butyl 4-oxo-1-piperidine carboxylate (10 g, 0.05 mol) in trifluoroacetic acid (10 mL) was stirred rt overnight and concentrated to give a pale yellow solid (11.26 g, crude). MS (Electron spray) 100 (MH^+), free amine; ^1H NMR (300 MHz, CD_3OD) δ 3.27-3.12 (m, 4H), 2.01-1.86 (m, 4H).

Intermediate E

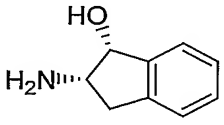
trans-1-Amino-2-hydroxyindan



This compound was prepared as described by Thompson et al., (J. Med. Chem. 35:1685-1701, 1992). To 1 liter of 12 N NH_4OH cooled to 0°C was added 50 g (0.235 mol) of 2-bromo-1-indanol. After stirring for 30 minutes, the mixture was allowed to warm, and then stirred for 24 hours. The mixture was concentrated under reduced pressure to remove excess ammonia and then allowed to stand open at rt overnight. The mixture was made basic (pH >10) by addition of 20% KOH, cooled in an ice bath, and filtered. After the residue was dried in a vacuum oven at 60°C overnight, the desired product was obtained as a tan solid (24 g, 69%).

Intermediate F

cis-1-Hydroxy-2-aminoindan

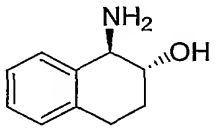


Following the procedure described in Tetrahedron: Asymmetry 7:1559-1562, 1996, trans-2-bromo-1-indanol (500 mg, 2.35 mmol) was dissolved in DMF (5 mL) and sodium azide (305

mg, 4.69 mmol) was added dropwise. The mixture was stirred at rt for 1 h, and then heated to 70°C and stirred for an additional 18 h. The mixture was cooled, water was added, and extracted with ether. The ether was removed and the crude (412 mg) was dissolved in THF (15 mL). This solution was added to Pd/C (41 mg) and stirred under hydrogen at rt for 3 days. The reaction mixture was filtered and the filtrate was concentrated down to provide the desired product, which was used without purification.

Intermediate *G*

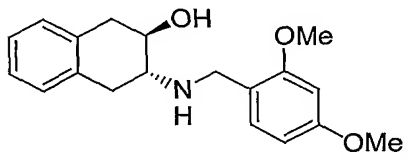
trans-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene



This compound was prepared from dihydronaphthalene according to the procedures described by Bellucci et al., (Tetrahedron: Asymmetry 8:895-902, 1997).

Intermediate H

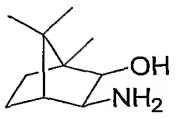
trans-(2R,3R)-3-[(2,4-Dimethoxybenzyl)amino]-1,2,3,4-tetrahydro-2-naphthalenol



This compound was prepared by following the procedure described by Efange et al., (J. Med. Chem. 40:3905-3914, 1997).

Intermediate I

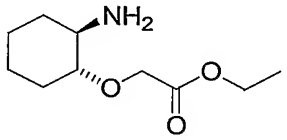
(1S,2R,3S,4R)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol



This compound, and its enantiomer, were obtained by $LiAlH_4$ reduction of the respective camphorquinone 3-oximes, by the procedure described by Gawley and Zhang, (J. Org. Chem. 61:8103-8112, 1996).

Intermediate J

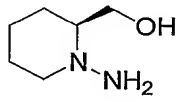
Ethyl [(trans-2-aminocyclohexyl)oxy]acetate



To a solution of trans-2-amino-cyclohexanol hydrochloride (455 mg, 3.0 mmol) in THF (7 mL) was added sodium hydride (78 mg, 3.25 mmol) under argon. The mixture was stirred at rt for 12 h before ethyl bromoacetate (500 mg, 3.0 mmol) was added, and the solution was stirred at rt for another 12 h. After filtration, the solution was concentrated and the residue taken up in CH_2Cl_2 and washed with brine. The organic layer was separated and concentrated. The residue was purified by flash chromatography over silica gel (ethyl acetate) to afford the desired product (51 mg, 8.5% yield): LC-MS *m/z* 202.2 (MH^+), retention time 0.73 min (method 1); Rf = 0.23 (ethyl acetate).

Intermediate K

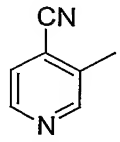
[(2S)-1-Amino-2-piperidinyl]methanol



[(2S)-1-Amino-2-piperidinyl]methanol was prepared according to the method described by Rosling et al., (Heterocycles 95-106, 1997). In a similar manner were prepared [(2R)-1-amino-2-piperidinyl]-methanol, [(2S)-1-amino-2-pyrrolidinyl]methanol, and [(2R)-1-amino-2-pyrrolidinyl]methanol.

Intermediate L

3-Methylisonicotinonitrile



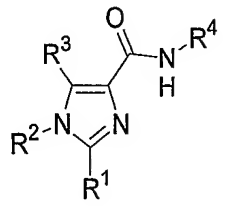
This nitrile was synthesized the procedure described by van den Haak et al., (J. Heterocycl. Chem. 18:1349-1352, 1981.

Summary of Examples

Using appropriate starting materials and the experimental procedures described above for Examples 1-49 and Intermediates A-L, the following compounds in Tables 1-18 were prepared. It will be understood by those skilled in the art that some minor modifications to the referenced procedures may have been made, but such modifications do not significantly affect the results of the preparation.

LC-MS characterization of compounds, as listed in the tables, was carried out by using the instrumentation and methods set forth above.

Table 1



Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
1	2,3-Cl_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2,3-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	449.1		3.05	1	8
2	2,4-Cl_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	449.3	0.47 (EtOAc)	3.14	1	13,14
3	2,4-Cl_2-Ph	4-F-Ph	H	1-piperidinyl	1-(4-fluorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	433.3	0.20 (33% EtOAc in Hexane)	2.89	1	15
4	2,4-Cl_2-Ph	4-I-Ph	H	1-piperidinyl	1-(4-iodophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	541.0		3.24	1	13,14
5	2,4-Cl_2-Ph	4-MeO-Ph	H	1-piperidinyl	1-(4-methoxyphenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	445.3	0.53 (EtOAc)	2.92	1	10

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
6	2,4-Cl_2-Ph	4-Me-Ph	H	1-piperidinyl	1-(4-methylphenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	429.3	0.25 (75% EtOAc in Hexane)	2.96	1	15
7	2,4-F_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	417.2	0.35 (EtOAc)	2.80	1	8
8	2,4-Me_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	409.3	0.62 (EtOAc)	2.77	1	10
9	2,4-Me_2-Ph	4-Cl-Ph	Me	1-piperidinyl	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	423.2		2.89	1	8
10	2,5-Cl_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	449.1	0.34 (75% EtOAc in Hexane)	3.11	1	8
11	2-CF_3-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-N-(1-piperidinyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxamide hydrochloride	449.3	0.25 (90% EtOAc in Hexane)	2.95	1	13,14
12	2-Cl-4-F-Ph	4-F-Ph	H	1-piperidinyl	1-(4-fluorophenyl)-2-(2-chloro-4-fluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	417.3	0.33 (EtOAc)	2.69	1	10

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
13	2-Cl-Ph	2,4-F_2-Ph	H	1-piperidinyl	1-(2,4-difluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	417.2	0.18 (1:1 EtOAc/ Hexane)	2.64	1	13,14
14	2-Cl-Ph	2-Cl-4-F-Ph	H	1-piperidinyl	1-(2-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	433.2	0.20 (1:1 EtOAc/ Hexane)	2.74	1	13,14
15	2-Cl-Ph	3-Cl-Ph	H	1-piperidinyl	1-(3-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	415.8	0.15 (50% EtOAc in Hexane)	2.90	1	13,14
16	2-Cl-Ph	3-Cl-Ph	Pr	1-piperidinyl	1-(3-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide	457.2	0.37 (1:1 EtOAc/ Hexane)	2.98	1	13,14
17	2-Cl-Ph	4-Br-Ph	Et	1-piperidinyl	1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide	487.2	0.48 (EtOAc)	3.05	1	13,14
18	2-Cl-Ph	4-Br-Ph	Pr	1-piperidinyl	1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide	503.1	0.28 (1:1 EtOAc/ Hexane)	3.06	1	13,14
19	2-Cl-Ph	4-Cl-Ph	Br	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-bromo-1H-imidazole-4-carboxamide hydrochloride	493.0		2.64	2	13,14

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
20	2-Cl-Ph	4-Cl-Ph	Bu	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide hydrochloride	471.3		2.88	2	13,14
21	2-Cl-Ph	4-Cl-Ph	Cl	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-chloro-1H-imidazole-4-carboxamide	451.2	0.16 (50% EtOAc in Hexane)	3.07	1	10
22	2-Cl-Ph	4-Cl-Ph	cyclopropyl	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-cyclopropyl-1H-imidazole-4-carboxamide hydrochloride	455.2		2.94	2	13,14
23	2-Cl-Ph	4-Cl-Ph	Et	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide	443.6	0.21 (60% EtOAc in Hexane)	2.91	1	8
24	2-Cl-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	415.1	0.25 (75% EtOAc in Hexane)	2.88	1	13,14
25	2-Cl-Ph	4-Cl-Ph	H	2,6-dimethyl-1-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,6-dimethyl-1-piperidinyl)-1H-imidazole-4-carboxamide	443.3	0.20 (50% EtOAc in Hexane)	2.94	1	13,14
26	2-Cl-Ph	4-Cl-Ph	H	(2S)-2-(hydroxymethyl)-1-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(hydroxymethyl)-1-piperidinyl]-1H-imidazole-4-carboxamide	445.1	0.37 (EtOAc)	2.93	1	8

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
27	2-Cl-Ph	4-Cl-Ph	H	(2R)-2-(hydroxymethyl)-1-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(hydroxymethyl)-1-piperidinyl]-1H-imidazole-4-carboxamide	445.6	0.40 (0.2% MeOH in EtOAc)	2.94	1	13,14
28	2-Cl-Ph	4-Cl-Ph	iPr	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-isopropyl-1H-imidazole-4-carboxamide hydrochloride	457.2		3.23	2	13,14
29	2-Cl-Ph	4-Cl-Ph	Me	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide	429.2	0.33 (EtOAc)	2.97	1	6
30	2-Cl-Ph	4-Cl-Ph	Pr	1-piperidinyl	1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide	457.7	0.2 (40% EtOAc in Hexane)	3.04	1	8
31	2-Cl-Ph	4-EtNHCONH-Ph	Me	1-piperidinyl	2-(2-chlorophenyl)-1-(4-{[(ethylamino)carbonyl]amino}phenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate	481.4		2.35	1	46
32	2-Cl-Ph	4-F-Ph	H	1-piperidinyl	1-(4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	399.3	0.15 (50% EtOAc in Hexane)	2.61	1	13,14
33	2-Cl-Ph	4-F-Ph	Pr	1-piperidinyl	1-(4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide	441.2	0.23 (1:1 EtOAc/ Hexane)	2.84	1	13,14

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
34	2-Cl-Ph	4-iPr-Ph	Et	1-piperidinyl	1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide	451.2	0.4 (2:1 EtOAc/ Hexane)	3.06	1	13,14
35	2-Cl-Ph	4-MeCONH-Ph	Me	1-piperidinyl	1-[4-(acetylamino)phenyl]-2-(2-chlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate	452.3		2.31	1	47
36	2-Cl-Ph	4-MeO-Ph	H	1-piperidinyl	1-(4-methoxyphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	411.3	0.29 (EtOAc)	2.62	1	13,14
37	2-Cl-Ph	4-MeO-Ph	Pr	1-piperidinyl	1-(4-methoxyphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide	453.1	0.19 (1:1 EtOAc/ Hexane)	2.84	1	13,14
38	2-Cl-Ph	4-Me-Ph	H	1-piperidinyl	1-(4-methylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	395.3	0.43 (EtOAc)	2.77	1	10
39	2-Cl-Ph	4-$MeSO_2$NH-Ph	Me	1-piperidinyl	2-(2-chlorophenyl)-5-methyl-1-{4-[(methylsulfonyl)amino]phenyl}-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate	488.4		2.29	1	48
40	2-Cl-Ph	4-$MeSO_2$-Ph	Me	1-piperidinyl	2-(2-chlorophenyl)-5-methyl-1-[4-(methylsulfonyl)phenyl]-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	473.6	0.25 (EtOAc)	2.45	1	13,14

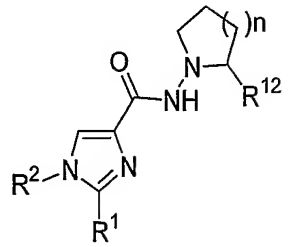
Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
41	2-Cl-Ph	4-NO_2-Ph	Me	1-piperidinyl	2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	440.3	0.47 (EtOAc)	2.68	1	8
42	2-Cl-Ph	Ph	H	1-piperidinyl	2-(2-chlorophenyl)-1-phenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	381.4	0.19 (75% EtOAc in Hexane)	2.64	1	13,14
43	2-Et-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	409.2	0.2 (50% EtOAc in Hexane)	2.95	1	8
44	2-MeO-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	411.3	0.38 (75% EtOAc in Hexane)	2.73	1	8
45	2-Me-Ph	2-Me-Ph	H	1-piperidinyl	1-(2-methylphenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	375.4	0.28 (75% EtOAc in Hexane)	2.68	1	13,14
46	2-Me-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	395.3	0.56 (EtOAc)	2.83	1	8
47	2-Me-Ph	4-Me-Ph	H	1-piperidinyl	1-(4-methylphenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	375.4	0.17 (50% EtOAc in Hexane)	2.66	1	13,14

Table 1

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
48	2-NO_2-Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-(2-nitrophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	426.4	0.20 (80% EtOAc in Hexane)	2.60	1	13,14
49	4-Br-Ph	2,4-Cl_2-Ph	H	1-piperidinyl	2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	495.0		3.23	1	13,14
50	4-Cl-Ph	2,4-Cl_2-Ph	H	1-piperidinyl	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride	451.1		3.19	1	13,14
51	4-I-Ph	2,4-Cl_2-Ph	H	1-piperidinyl	2-(4-iodophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	541.0		3.30	1	13,14
52	Ph	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-phenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	381.3		2.65	1	8
53	Ph	Ph	H	1-piperidinyl	1,2-diphenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	347.2		3.50	1	13,14

Table 2



Entry No.	R^1	R^2	n	R^{12}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
54	2-MeO-Ph	4-Cl-Ph	1	H	1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide	397.3	0.2 (75% EtOAc in hexane)	2.46	1	13,14
55	2-Cl-Ph	4-Cl-Ph	1	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide trifluoroacetate	401.2	0.4 (5% MeOH in EtOAc)	2.55	1	8
56	2-Cl-Ph	4-Cl-Ph	1	(R)-CH_2OMe	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate	445.2	0.4 (35% EtOAc in hexane)	2.84	1	8
57	2-Cl-Ph	4-Cl-Ph	1	(S)-CH_2OMe	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate	445.2	0.4 (5% MeOH in EtOAc)	2.89	1	8

Table 2

Entry No.	R^1	R^2	n	R^{12}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
58	2-MeO-Ph	4-Cl-Ph	1	(R)-CH_2OMe	1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide	441.3	0.25 (EtOAc)	2.72	1	13,14
59	2-MeO-Ph	4-Cl-Ph	1	(S)-CH_2OMe	1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide	441.3	0.25 (EtOAc)	2.73	1	13,14
60	2-MeO-Ph	4-Cl-Ph	3	H	N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide	425..3	0.5 (50% EtOAc in hexane)	2.72	1	13,14
61	2,4-Cl_2-Ph	4-Cl-Ph	1	H	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide trifluoroacetate	435.1	0.36 (EtOAc)	2.78	1	13,14
62	2,4-Cl_2-Ph	4-Cl-Ph	1	(R)-CH_2OMe	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate	479.2	0.36 (EtOAc)	3.13	1	13,14
63	2-Me-Ph	4-Cl-Ph	1	H	1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide	381.3	0.2 (EtOAc)	2.48	1	13,14

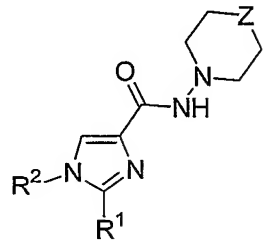
Table 2

Entry No.	R^1	R^2	n	R^{12}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
64	2-Me-Ph	4-Cl-Ph	1	(R)-CH_2OMe	1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methylphenyl)-1H-imidazole-4-carboxamide	425.3	0.33 (EtOAc)	2.78	1	13,14
65	2-Me-Ph	4-Cl-Ph	1	(S)-CH_2OMe	1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methylphenyl)-1H-imidazole-4-carboxamide	425.3	0.33 (EtOAc)	2.79	1	13,14
66	2-Me-Ph	4-Cl-Ph	3	H	N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2-methylphenyl)-1H-imidazole-4-carboxamide	409.3	0.57 (EtOAc)	2.82	1	13,14
67	2,4-Me_2-Ph	4-Cl-Ph	1	H	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide	395.3	0.25 (EtOAc)	2.61	1	13,14
68	2,4-Me_2-Ph	4-Cl-Ph	1	(R)-CH_2OMe	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide	439.3	0.32 (EtOAc)	2.90	1	13,14
69	2,4-Me_2-Ph	4-Cl-Ph	1	(S)-CH_2OMe	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide	439.3	0.32 (EtOAc)	2.91	1	13,14

Table 2

Entry No.	R^1	R^2	n	R^{12}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
70	2,4-Me_2-Ph	4-Cl-Ph	3	H	N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxamide	423.3	0.6 (EtOAc)	2.93	1	13,14
71	2,4-Cl_2-Ph	4-Me-Ph	3	H	N-(1-azepanyl)-2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-1H-imidazole-4-carboxamide trifluoroacetate	443.3	0.4 (75% EtOAc in hexane)	3.03	1	15
72	2,4-Cl_2-Ph	4-F-Ph	3	H	N-(1-azepanyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide trifluoroacetate	447.3	0.4 (75% EtOAc in hexane)	2.96	1	15
73	2-Cl-Ph	4-Cl-Ph	1	(S)-CH_2OMe	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide	431.1	0.24 (EtOAc)	2.81	1	8
74	2-Cl-Ph	4-Cl-Ph	1	(R)-CH_2OMe	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(hydroxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide	431.2	0.35 (EtOAc)	2.71	1	13,14

Table 3



Entry No.	R^1	R^2	Z	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
75	2-Cl-Ph	4-Cl-Ph	O	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	417.0	0.45 (7% MeOH in CH2Cl2)	3.32	1	8
76	2-MeO-Ph	4-Cl-Ph	O	1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	413.2	0.22 (75% EtOAc in hexane)	2.55	1	13,14
77	2,4-Cl_2-Ph	4-Cl-Ph	O	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	453.2	0.57 (50% EtOAc in hexane)	3.03	1	13,14
78	2,4-F-Ph	4-Cl-Ph	O	1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	419.2	0.28 (5% MeOH in EtOAc)	2.73	1	8

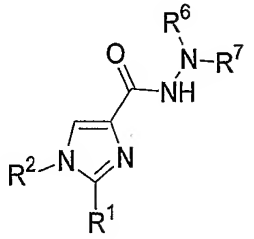
Table 3

Entry No.	R^1	R^2	Z	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
79	2-Me-Ph	4-Cl-Ph	O	1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	397.3	0.18 (EtOAc)	2.63	1	13,14
80	2,4-Me-Ph	4-Cl-Ph	O	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide	411.3	0.19 (EtOAc)	2.77	1	13,14
81	2,4-Me-Ph	4-Cl-Ph	NMe	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate)	421.2	0.6 (20% 2M NH3/MeOH in EtOAc)	2.82	1	13,14
82	2,4-Cl_2-Ph	4-Me-Ph	NMe	2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate)	444.3		2.29	1	15
83	2,4-Cl_2-Ph	4-F-Ph	NMe	2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate)	448.2		2.21	1	15

Table 3

Entry No.	R^1	R^2	Z	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
84	2-Et-Ph	4-Cl-Ph	NMe	1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide	424.3	0.62 (25% 2M NH3/MeOH in EtOAc)	2.28	1	13,14

Table 4



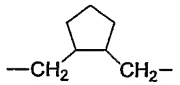
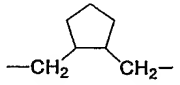
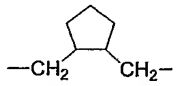
Entry No.	R^1	R^2	R^6	R^7	IUPAC name	MS m/z [MH+]	HPLC Retention time (min.)	HPLC method	Synthesis Method of Ex. No.
85	2,4-Cl_2-Ph	4-Cl-Ph	Me	Me	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N',N'-dimethyl-1H-imidazole-4-carbohydrazide	409.0	2.9	1	8
86	2,4-Cl_2-Ph	4-MeO-Ph			2-(2,4-dichlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide hydrochloride	471	2.98	2	10,11,12
87	2-Me-Ph	4-Cl-Ph			1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-2-(2-methylphenyl)-1H-imidazole-4-carboxamide hydrochloride	421	2.82	2	10,11,12
88	2,4-Cl_2-Ph	4-F-Ph			2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride	459	3.38	2	10,11,12

Table 4

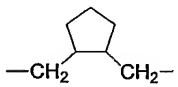
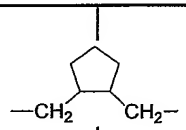
Entry No.	R^1	R^2	R^6	R^7	IUPAC name	MS m/z [MH+]	HPLC Retention time (min.)	HPLC method	Synthesis Method of Ex. No.
89	2,4-Cl_2-Ph	4-Cl-Ph			1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride	475	3.16	2	10,11,12
90	2-Cl-Ph	4-Cl-Ph			2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride	441	3.23	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
91	2,4-Cl_2-Ph	4-Cl-Ph	H	2-CF_3-Ph	H	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	525	0.4 (20% EtOAc/ Hexane)	4.25	2	10,11,12
92	2,4-Cl_2-Ph	4-Cl-Ph	H	Ph	Me	2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-N''-methyl-N''-phenyl-1H-imidazole-4-carbohydrazide	473	0.6 (50% EtOAc in Hexane)	3.70	1	8
93	2,4-Cl_2-Ph	4-Cl-Ph	H	3-Cl-4-F-Ph	H	N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	509		4.13	2	10,11,12
94	2,4-Cl_2-Ph	4-F-Ph	H	2-Cl-Ph	H	N'-(2-chlorophenyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	475		3.40	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
95	2,4-Cl_2-Ph	4-F-Ph	H	3-Cl-4-F-Ph	H	N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	493		3.39	2	10,11,12
96	2,4-Cl_2-Ph	4-F-Ph	H	2-Cl-4-CF_3-Ph	H	N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	543		3.66	2	10,11,12
97	2,4-Cl_2-Ph	4-MeO-Ph	H	3-Cl-4-F-Ph	H	N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carbohydrazide hydrochloride	505		3.36	2	10,11,12
98	2,4-F_2-Ph	4-Cl-Ph	H	Ph	Me	1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	439	0.27 (50% EtOAc in Hexane)	3.39	1	8
99	2,4-Me_2-Ph	4-Cl-Ph	H	Ph	Me	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	431	0.64 (50% EtOAc in Hexane)	3.48	1	8

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
100	2,5-Cl_2-Ph	4-Cl-Ph	H	2-CF_3-Ph	H	1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	525	0.41 (25% EtOAc in Hexane)	3.76	1	8
101	2,5-Cl_2-Ph	4-Cl-Ph	H	3-CF_3-Ph	H	1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	526	0.2 (33% EtOAc in Hexane)	3.69	1	8
102	2,5-Cl_2-Ph	4-Cl-Ph	H	4-CF_3-Ph	H	1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	526	0.2 (33% EtOAc in Hexane)	3.70	1	8
103	2-CF_3-Ph	4-Cl-Ph	H	4-CF_3-Ph	H	1-(4-chlorophenyl)-2-[2-(trifluoromethyl)phenyl]-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate	525		3.38	2	10,11,12
104	2-CF_3-Ph	4-Cl-Ph	H	2-CF_3-Ph	H	1-(4-chlorophenyl)-N',2-bis[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	525		3.97	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
105	2-Cl-Ph	4-Br-Ph	Et	2-CF_3-Ph	H	1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	563	0.24 (20% EtOAc in Hexane)	3.88	1	8
106	2-Cl-Ph	4-Br-Ph	Et	4-CF_3-Ph	H	1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	563	0.27 (33% EtOAc in Hexane)	3.82	1	8
107	2-Cl-Ph	4-Br-Ph	Et	2-Cl-4-CF_3-Ph	H	1-(4-bromophenyl)-2-(2-chlorophenyl)-N'-[2-chloro-4-(trifluoromethyl)phenyl]-5-ethyl-1H-imidazole-4-carbohydrazide	597	0.18 (20% EtOAc in Hexane)	3.98	1	6
108	2-Cl-Ph	4-Cl-Ph	Cyclopropyl	2-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	531		3.61	2	13,14
109	2-Cl-Ph	4-Cl-Ph	Cyclopropyl	4-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	531		3.62	2	13,14

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
110	2-Cl-Ph	4-Cl-Ph	Et	2,4-Cl_2-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carbohydrazide	519	0.6 (33% EtOAc in Hexane)	4.02	1	6
111	2-Cl-Ph	4-Cl-Ph	Et	2,4-$(CF_3)_2$-Ph	H	N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carbohydrazide	587	0.47 (30% EtOAc in Hexane)	3.75	1	8
112	2-Cl-Ph	4-Cl-Ph	H	2-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	491		4.02	2	10,11,12
113	2-Cl-Ph	4-Cl-Ph	H	3-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	491		3.99	2	10,11,12
114	2-Cl-Ph	4-Cl-Ph	H	4-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	491		3.99	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
115	2-Cl-Ph	4-Cl-Ph	H	2-CF_3-4-Cl-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	525		3.55	2	10,11,12
116	2-Cl-Ph	4-Cl-Ph	H	Ph	Me	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	437	0.5 (60% EtOAc in Hexane)	3.85	1	8
117	2-Cl-Ph	4-Cl-Ph	H	Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-phenyl-1H-imidazole-4-carbohydrazide hydrochloride	423		3.07	2	10,11,12
118	2-Cl-Ph	4-Cl-Ph	H	2,4-Cl_2-Ph	H	N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	492		3.55	2	10,11,12
119	2-Cl-Ph	4-Cl-Ph	H	2,4-F_2-Ph	H	N'-(2,4-difluorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	460		3.07	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
120	2-Cl-Ph	4-Cl-Ph	H	2-Cl-4-CN-Ph	H	N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	482		3.03	2	10,11,12
121	2-Cl-Ph	4-Cl-Ph	H	2-Cl-Ph	H	N'-(2-chlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	457		3.18	2	10,11,12
122	2-Cl-Ph	4-Cl-Ph	H	3-Cl-4-F-Ph	H	N'-(3-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	475		3.28	2	10,11,12
123	2-Cl-Ph	4-Cl-Ph	H	2-Me-4-Cl-Ph	H	N'-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	471		3.36	2	10,11,12
124	2-Cl-Ph	4-Cl-Ph	H	2,4-$(CF_3)_2$-Ph	H	N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	559		3.62	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
125	2-Cl-Ph	4-Cl-Ph	H	2-Cl-4-CF_3-Ph	H	N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	525		3.55	2	10,11,12
126	2-Cl-Ph	4-Cl-Ph	Me	2,4-Cl_2-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide	505	0.71 (50% EtOAc in Hexane)	3.88	1	6
127	2-Cl-Ph	4-Cl-Ph	Pr	2,4-Cl_2-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide	533		3.87	2	10,11,12
128	2-Cl-Ph	4-Cl-Ph	Pr	2,4-Cl_2-Ph	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide hydrochloride	533		3.87	2	10,11,12
129	2-Cl-Ph	4-Cl-Ph	Pr	2,4-$(CF_3)_2$-Ph	H	N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide hydrochloride	601		4.00	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
130	2-Cl-Ph	4-F-Ph	H	2-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-fluorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	475		3.68	2	10,11,12
131	2-Cl-Ph	4-F-Ph	H	4-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-fluorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	475		3.27	2	10,11,12
132	2-Cl-Ph	4-Me-Ph	H	2-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate	471		4.02	2	10,11,12
133	2-Cl-Ph	4-Me-Ph	H	3-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate	471		3.88	2	10,11,12
134	2-Cl-Ph	4-Me-Ph	H	4-CF_3-Ph	H	2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride	471		3.28	2	10,11,12

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
135	2-Cl-Ph	4-NO_2-Ph	Me	2-CF_3-Ph	H	2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	516	0.4 (33% EtOAc in Hexane)	3.56	1	8
136	2-Et-Ph	4-Cl-Ph	H	Ph	Me	1-(4-chlorophenyl)-2-(2-ethylphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	431	0.68 (50% EtOAc in Hexane)	3.52	1	8
137	2-MeO-Ph	4-Cl-Ph	H	Ph	Me	2-(2-methoxyphenyl)-1-(4-chlorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	433	0.45 (50% EtOAc in Hexane)	3.26	1	8
138	2-Me-Ph	4-Cl-Ph	H	2-CF_3-Ph	H	1-(4-chlorophenyl)-2-(2-methylphenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide	471	0.4 (20% EtOAc/ Hexane)	3.89	2	10,11,12
139	2-Me-Ph	4-Cl-Ph	H	Ph	Me	1-(4-chlorophenyl)-2-(2-methylphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide	417	0.54 (50% EtOAc in Hexane)	3.34	1	8

Table 5

Entry No.	R^1	R^2	R^3	R^6	R^7	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
140	2-Me-Ph	4-Cl-Ph	H	3-Cl-4-F-Ph	H	N'-(3-chloro-4-fluorophenyl)-2-(2-methylphenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride	455		3.78	2	10,11,12

Table 6

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
141	4-Br-Ph	2,4-Cl_2-Ph	H	H	2-(4-bromophenyl)-N-cyclohexyl-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide	494.0		3.96	1	8
142	4-Cl-Ph	2,4-Cl_2-Ph	H	H	2-(4-chlorophenyl)-N-cyclohexyl-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide					13, 14
143	Ph	Ph	H	H	N-cyclohexyl-1,2-diphenyl-1H-imidazole-4-carboxamide	346.2		3.22	1	8
144	4-I-Ph	2,4-Cl_2-Ph	H	H	N-cyclohexyl-1-(2,4-dichlorophenyl)-2-(4-iodophenyl)-1H-imidazole-4-carboxamide	540.0		4.03	1	8

Table 6

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
145	2,4-Cl_2-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide	448.2	0.57 (50% EtOAc in hexane)	3.84	1	13, 14
146	2-Cl-Ph	4-Cl-Ph	H	H	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-cyclohexyl-1H-imidazole-4-carboxamide	414.2	0.21 (35% EtOAc in hexane)	3.48	1	8
147	2-MeO-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide	410.2	0.5 (50% EtOAc in hexane)	3.25	1	13, 14
148	2-Me-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2-methylphenyl)-1H-imidazole-4-carboxamide	394.2	0.64 (50% EtOAc in hexane)	3.44	1	13, 14
149	2,4-Me_2-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxamide	408.3	0.68 (50% EtOAc in hexane)	3.56	1	13, 14
150	2,4-Cl_2-Ph	4-MeO-Ph	H	H	N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	444.2		3.55	1	8

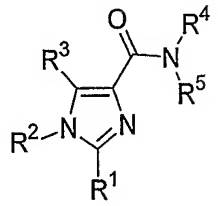
Table 6

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
151	2-F-Ph	$2\text{-}NO_2$-Ph	Me	H	N-cyclohexyl-2-(2-fluorophenyl)-5-methyl-1-(2-nitrophenyl)-1H-imidazole-4-carboxamide	423.2	0.11 (33% EtOAc in hexane)	3.22	1	8
152	$2,4\text{-}Cl_2$-Ph	4-Me-Ph	H	H	N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-1H-imidazole-4-carboxamide	428.2	0.6 (30% EtOAc in hexane)	3.76	1	15
153	$2,4\text{-}Cl_2$-Ph	4-F-Ph	H	H	N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide	432.2	0.17 (30% EtOAc in hexane)	3.62	1	15
154	$2,4\text{-}F_2$-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-difluorophenyl)-1H-imidazole-4-carboxamide	416.3	0.22 (30% EtOAc in hexane)	3.47	1	15
155	2-Cl-Ph	$4\text{-}NO_2$-Ph	Me	H	2-(2-chlorophenyl)-N-cyclohexyl-5-methyl-1-(4-nitrophenyl)-1H-imidazole-4-carboxamide	439.2		3.41	1	8
156	2-Et-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2-ethylphenyl)-1H-imidazole-4-carboxamide	408.3	0.72 (50% EtOAc in hexane)	3.62	1	13, 14

Table 6

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
157	2-Cl-Ph	4-Cl-Ph	H	Me	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-cyclohexyl-N-methyl-1H-imidazole-4-carboxamide	428.2	0.19 (50% EtOAc in hexane)	3.47	1	8
158	2-Cl-Ph	4-F-Ph	H	H	2-(2-chlorophenyl)-N-cyclohexyl-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide	398.3	0.52 (50% EtOAc in hexane)	3.22	1	10, 11, 12
159	2-Cl-Ph	4-MeO-Ph	H	H	2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	410.3	0.47 (50% EtOAc in hexane)	3.16	1	10, 11, 12
160	2-Cl-Ph	4-Me-Ph	H	H	2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methylphenyl)-1H-imidazole-4-carboxamide	394.3	0.6 (50% EtOAc in hexane)	3.31	1	10, 11, 12
161	Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-phenyl 1H-imidazole-4-carboxamide	380.3		3.35	1	8
162	2,5-Cl_2-Ph	4-Cl-Ph	H	H	1-(4-chlorophenyl)-N-cyclohexyl-2-(2,5-dichlorophenyl)-1H-imidazole-4-carboxamide	448.6	0.15 (25% EtOAc in hexane)	3.83	1	8

Table 7



Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
163	4-Cl-Ph	2,4-Cl_2-Ph	H	—$(CH_2)_5$—		1-{[2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}piperidine	436.1		3.59	1	13, 14
164	4-Cl-Ph	2,4-Cl_2-Ph	H	Me	Me	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N,N-dimethyl-1H-imidazole-4-carboxamide					13, 14
165	2,4-Cl_2-Ph	4-Me-Ph	H	—$(CH_2)_5$—		1-{[2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-1H-imidazol-4-yl]carbonyl}piperidine	414.3	0.2 (50% EtOAc in hexane)	3.34	1	9
166	2,4-Cl_2-Ph	4-MeO-Ph	H	—CH_2CH=$CH(Ph)CH_2CH_2$—		1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine	522		3.53	2	10, 11, 12

Table 7

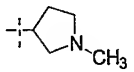
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
167	2,4-Cl_2-Ph	4-Cl-Ph	H	—CH_2CH=$CH(Ph)CH_2CH_2$—		1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine	526		3.33	2	10, 11, 12
168	2-Me-Ph	4-Cl-Ph	H	—CH_2CH=$CH(Ph)CH_2CH_2$—		1-{[1-(4-chlorophenyl)-2-(2-methylphenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine	472		2.9	2	10, 11, 12
169	2,4-Cl_2-Ph	4-F-Ph	H	—CH_2CH=$CH(Ph)CH_2CH_2$—		1-{[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine	510		3.05	2	10, 11, 12
170	2-Cl-Ph	4-Cl-Ph	H	—CH_2CH=$CH(Ph)CH_2CH_2$—		1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine	492		3.47	2	10, 11, 12
171	2-Cl-Ph	4-Cl-Ph	H	—$(CH_2)_3CH(CH_2OH)CH_2$—		(1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-3-piperidinyl)methanol	430		2.52	2	10, 11, 12
172	2-Cl-Ph	4-Cl-Ph	H	Me		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methyl-N-(1-methyl-3-pyrrolidinyl)-1H-imidazole-4-carboxamide hydrochloride	429		2.15	2	10, 11, 12

Table 7

Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
173	2-Cl-Ph	4-Cl-Ph	H	—$(CH_2)_2CH[N(Et)_2]CH_2$—		N-(1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-3-pyrrolidinyl)-N,N-diethylamine hydrochloride	457		2.08	2	10, 11, 12
174	2,4-Cl_2-Ph	4-Cl-Ph	H	Me		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-methyl-N-[(1R,2R)-2-(methylamino)cyclohexyl]-1H-imidazole-4-carboxamide hydrochloride	491.2		2.41	2	10, 11, 12
175	2,4-Cl_2-Ph	4-Cl-Ph	H	Me		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-methyl-N-[(1S,2S)-2-(methylamino)cyclohexyl]-1H-imidazole-4-carboxamide hydrochloride	491.2		2.34	2	10, 11, 12
176	2-Cl-Ph	4-Cl-Ph	H	—$(CH_2)_2S(CH_2)_2$—		4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}thiomorpholine	418.6	0.3 (50% EtOAc in hexane)	3.15	1	13, 14
177	2-Cl-Ph	4-Cl-Ph	H	—$(CH_2)_2C(=O)(CH_2)_2$—		1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-piperidinone	414.1	0.29 (50% EtOAc in hexane)	2.75	1	13, 14
178	2-Cl-Ph	4-Cl-Ph	H	—$(CH_2)_2\overset{O}{\overset{\|}{S}}(CH_2)_2$—		4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}thiomorpholine 1-oxide	434.5	0.47 (1:5 EtOAc/ Hexane)	2.55	1	13, 14

Table 7

Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
179	2-Cl-Ph	4-Cl-Ph	Et	$-(CH_2)_2C(=O)(CH_2)_2-$		1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-piperidinone	442.1	0.06 (1:1 EtOAc/ Hexanes)	2.99	1	13, 14
180	2-Cl-Ph	4-Cl-Ph	n-Pr	$-(CH_2)_2C(=O)(CH_2)_2-$		1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-piperidinone	456.1	0.06 (1:1 EtOAc/ Hexanes)	3.13	1	13, 14
181	2-Cl-Ph	4-Cl-Ph	H	Me	OMe	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide	376.1	0.22 (EtOAc)	2.77	1	13, 14
182	2-Cl-Ph	2,4-F_2-Ph	H	$-(CH_2)_5-$		1-{[2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-1H-imidazol-4-yl]carbonyl}piperidine	402.2	0.36 (2:1 EtOAc/ Hexanes)	2.97	1	13, 14
183	2-Cl-Ph	4-*i*Pr-Ph	Et	$-(CH_2)_5-$		1-{[2-(2-chlorophenyl)-5-ethyl-1-(4-isopropylphenyl)-1H-imidazol-4-yl]carbonyl}piperidine	436.1	0.06 (1:1 EtOAc/ Hexanes)	3.36	1	13, 14

Table 8

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
184	2-MeO-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-phenyl-1H-imidazole-4-carboxamide	404.1	0.83 (50% EtOAc in hexane)	3.42	1	13, 14
185	2,4-Cl_2-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-phenyl-1H-imidazole-4-carboxamide	444.1	0.89 (50% EtOAc in hexane)	3.87	1	13, 14
186	2-Cl-Ph	4-Cl-Ph	4H-1,2,4-triazol-4-yl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide	399.1	<0.1 (15% MeOH in EtOAc)	2.71	1	8
187	2-Cl-Ph	4-Cl-Ph	Ph	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-phenyl-1H-imidazole-4-carboxamide	408.1	0.4 (35% EtOAc in hexane)	3.54	1	8

Table 8

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
188	2,4-F_2-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-phenyl-1H-imidazole-4-carboxamide	410.1	0.5 (35% EtOAc in hexane)	3.52	1	8
189	2-Me-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2-methylphenyl)-N-phenyl-1H-imidazole-4-carboxamide	388.1	0.86 (50% EtOAc in hexane)	3.52	1	13, 14
190	2,4-Me_2-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-phenyl-1H-imidazole-4-carboxamide	402.2	0.92 (50% EtOAc in hexane)	3.67	1	13, 14
191	2,4-Me_2-Ph	4-Cl-Ph	4H-1,2,4-triazol-4-yl	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide	393.1	0.19 (20% 2M NH3/MeOH in EtOAc)	2.87	1	13, 14
192	2,4-Me_2-Ph	4-Cl-Ph	3,5-dimethyl-4H-1,2,4-triazol-4-yl	1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide	424.2	0.26 (20% 2M NH3/MeOH in EtOAc)	2.37	1	13, 14
193	2,4-Cl_2-Ph	4-F-Ph	Ph	2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-phenyl-1H-imidazole-4-carboxamide	426.1	0.46 (30% EtOAc in hexane)	3.61	1	15

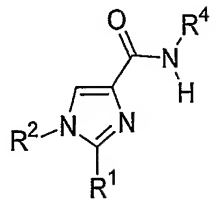
Table 8

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
194	2-Cl-Ph	4-Cl-Ph	3-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(3-pyridinyl)-1H-imidazole-4-carboxamide	409.3	0.25 (5% MeOH in EtOAc)	2.44	1	15
195	2-Cl-Ph	4-Cl-Ph	2-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyridinyl)-1H-imidazole-4-carboxamide	409.1	0.25 (5% MeOH in CH2Cl2)	2.99	1	15
196	2-Cl-Ph	4-Cl-Ph	4-Cl-Ph	2-(2-chlorophenyl)-N,1-bis(4-chlorophenyl)-1H-imidazole-4-carboxamide	442.1	0.65 (30% EtOAc in hexane)	3.79	1	15
197	2-Et-Ph	4-Cl-Ph	Ph	1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-phenyl-1H-imidazole-4-carboxamide	402.1	0.4 (50% EtOAc in hexane)	3.71	1	13, 14
198	2-Cl-Ph	4-Cl-Ph	4-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide	409.5	0.37 (EtOAc)	2.45	1	10, 11, 12
199	2-Cl-Ph	4-Cl-Ph	4-CF_3-3-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carboxamide	477.3	0.44 (50% EtOAc in hexane)	3.39	1	13, 14

Table 8

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
200	2-Cl-Ph	4-Cl-Ph	4-Me-3-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-methyl-3-pyridinyl)-1H-imidazole-4-carboxamide	423.3	0.31 (EtOAc)	2.41	1	8
201	2-Cl-Ph	4-Cl-Ph	4-pyrimidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyrimidinyl)-1H-imidazole-4-carboxamide hydrochloride	410.4	0.27 (50% EtOAc in hexane)	3.04	1	13, 14
202	2-Cl-Ph	4-Cl-Ph	2-pyrimidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyrimidinyl)-1H-imidazole-4-carboxamide	410.6	0.32 (50% EtOAc in hexane)	2.85	1	6
203	2-Cl-Ph	4-Cl-Ph	2-pyrazinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyrazinyl)-1H-imidazole-4-carboxamide	410.6	0.47 (75% EtOAc in hexane)	3.18	1	6
204	2-Cl-Ph	4-Cl-Ph	5-CF_3-2-pyridinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[5-(trifluoromethyl)-2-pyridinyl]-1H-imidazole-4-carboxamide	477.2	0.4 (25% EtOAc in hexane)	3.77	1	6

Table 9



Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
205	4-Cl-Ph	2,4-Cl_2-Ph	2-(1-piperidinyl)ethyl	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(1-piperidinyl)ethyl]-1H-imidazole-4-carboxamide	477				13, 14
206	4-Cl-Ph	2,4-Cl_2-Ph	2-(Et_2N)ethyl	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(diethylamino)ethyl]-1H-imidazole-4-carboxamide	465		2.54	1	13, 14
207	4-Cl-Ph	2,4-Cl_2-Ph	2-(Me_2N)ethyl	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(dimethylamino)ethyl]-1H-imidazole-4-carboxamide	437		2.46	1	8

Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
208	4-Cl-Ph	2,4-Cl_2-Ph	3-(Me_2N)-1-propyl	2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[3-(dimethylamino)propyl]-1H-imidazole-4-carboxamide	451		2.48	1	13, 14
209	2-Cl-Ph	4-Cl-Ph	endo-2-norbornyl	N-endo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	426	0.21 (40% EtOAc in hexane)	3.50	1	15
210	2-Cl-Ph	4-Cl-Ph	exo-2-norbornyl	N-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	426	0.19 (30% EtOAc in hexane)	3.49	1	15
211	2-Cl-Ph	4-Cl-Ph	1-propyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-propyl-1H-imidazole-4-carboxamide	374	0.5 (30% EtOAc in hexane)	3.10	1	15
212	2-Cl-Ph	4-Cl-Ph	3-pentyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-ethylpropyl)-1H-imidazole-4-carboxamide	402	0.21 (30% EtOAc in hexane)	3.33	1	13, 14

Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
213	2-Cl-Ph	4-Cl-Ph	1,7,7-trimethylbicyclo[2.2.1]hept-2-yl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-1H-imidazole-4-carboxamide	468	0.29 (30% EtOAc in hexane)	3.97	1	8
214	2-Cl-Ph	4-Cl-Ph	trans-2-($HOCH_2$)-cyclohexyl	trans-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1H-imidazole-4-carboxamide	444	30% EtOAc/ Hexane	3.51	2	10, 11, 12
215	2-Cl-Ph	4-Cl-Ph	2,3-dihydro-1,4-benzodioxin-2-yl-CH_2	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1H-imidazole-4-carboxamide	480		3.88	2	10, 11,12
216	2-Cl-Ph	4-Cl-Ph	2,4-Cl_2-benzyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,4-dichlorobenzyl)-1H-imidazole-4-carboxamide	490		4.21	2	10, 11,12
217	2-Cl-Ph	4-Cl-Ph	3-(1-pyrrolidinyl)-1-propyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-1H-imidazole-carboxamide hydrochloride	443		2.48	2	10, 11, 12

Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
218	2,4-Cl_2-Ph	4-Cl-Ph	3-(1-pyrrolidinyl)-1-propyl	1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-1H-imidazole-4-carboxamide	477	0.67 (40% 2M NH3/MeOH in EtOAc)	2.45	1	13, 14
219	2-CF_3-Ph	4-Cl-Ph	3-(1-pyrrolidinyl)-1-propyl	1-(4-chlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxamide	477		2.55	2	10, 11, 12
220	2-Cl-Ph	4-Cl-Ph	1-benzyl-4-piperidinyl	N-(1-benzyl-4-piperidinyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	505		2.66	2	10, 11, 12
221	2-Cl-Ph	4-Cl-Ph	1-CO_2Et-4-piperidinyl	ethyl 4-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}amino)-1-piperidinecarboxylate	487	0.25 (83% EtOAc in hexane)	3.01	1	13, 14
222	2,4-Cl_2-Ph	4-MeO-Ph	trans-2-($HOCH_2$)-cyclohexyl	trans-2-(2,4-dichlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	474		3.58	2	10, 11, 12

Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
223	2,4-Cl_2-Ph	4-MeO-Ph	1-benzyl-4-piperidinyl	N-(1-benzyl-4-piperidinyl)-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	535		2.74	2	10, 11, 12
224	2-Cl-Ph	4-Cl-Ph	4-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-piperidinyl)-1H-imidazole-4-carboxamide	415	0.25 (50% 2M NH3/MeOH in EtOAc)	2.22	1	37
225	2,4-Cl_2-Ph	4-MeO-Ph	cis-2-($HOCH_2$)-cyclohexyl	cis-2-(2,4-dichlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	474		3.69	2	10, 11, 12
226	2,4-Cl_2-Ph	4-MeO-Ph	cis-2-OH-cycloheptyl-CH_2	cis-2-(2,4-dichlorophenyl)-N-{2-hydroxycycloheptyl]methyl}-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	488		3.66	2	10, 11, 12
227	2,4-Cl_2-Ph	4-MeO-Ph	trans-2-OH-cyclohexyl-CH_2	trans-2-(2,4-dichlorophenyl)-N-{[2-hydroxycyclohexyl]methyl}-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	474		3.47	2	10, 11, 12

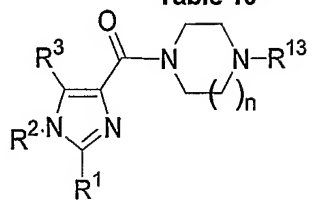
Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
228	2,4-Cl_2-Ph	4-MeO-Ph	3-exo-$HOCH_2$-2-exo-norbornyl	exo,exo-2-(2,4-dichlorophenyl)-N-[3-(hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	486		3.44	2	10, 11, 12
229	2-Cl-Ph	4-Cl-Ph	1-Me-4-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-methyl-4-piperidinyl)-1H-imidazole-4-carboxamide	429	0.31(90 % MeOH in 2M NH3 in MeOH	2.27	1	13, 14
230	2-Cl-Ph	4-Cl-Ph	1-(2-pyridinyl)-4-piperidinyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide	492	0.33 (33% EtOAc in hexane)	2.47	1	13, 14
231	2-Cl-Ph	4-Cl-Ph	trans-2-(acetyloxy)-cyclohexyl	trans-2-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}amino)cyclohexyl acetate	472	0.33 (50% EtOAc in hexane)	3.25	1	13, 14
232	2-Cl-Ph	4-Cl-Ph	1-benzyl-3-pyrrolidinyl	N-(1-benzyl-3-pyrrolidinyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide hydrochloride	491		2.34	2	10, 11, 12

Table 9

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis method of Ex. No.
233	2-Cl-Ph	4-Cl-Ph	1-Et-2-pyrrolidinyl-CH_2	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-1H-imidazole-4-carboxamide hydrochloride	443		2.26	2	10, 11, 12
234	2,4-Cl_2-Ph	4-Cl-Ph	(R,R)-2-amino-cyclohexyl	N-[(1R,2R)-2-aminocyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide hydrochloride	463		2.37	2	10, 11, 12
235	2,4-Cl_2-Ph	4-Cl-Ph	(S,S)-2-amino-cyclohexyl	N-[(1S,2S)-2-aminocyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide hydrochloride	463		2.34	2	10, 11, 12

Table 10



Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
236	2,4-Cl_2-Ph	4-Cl-Ph	H	1	2,3-Me_2-Ph	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,3-dimethylphenyl)piperazine	539	0.55 (50% EtOAc in hexane)	4.17	1	13, 14
237	2,4-Cl_2-Ph	4-Cl-Ph	H	1	2,4-F_2-Ph	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,4-difluorophenyl)piperazine	549	0.27 (60% EtOAc in hexane)	3.71	1	13, 14
238	2,4-Cl_2-Ph	4-Cl-Ph	H	1	2-CN-Ph	2-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile	536	0.73 (EtOAc)	3.69	1	13, 14

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
239	2,4-Cl_2-Ph	4-Cl-Ph	H	1	2-phenyl-ethyl	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-phenylethyl)piperazine	539	0.30 (2% MeOH in EtOAc)	2.79	1	13, 14
240	2,4-Cl_2-Ph	4-Cl-Ph	H	1	2-pyridinyl	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-pyridinyl)piperazine	512	0.6 (EtOAc)	2.48	1	10, 11, 12
241	2,4-Cl_2-Ph	4-Cl-Ph	H	1	3-CF_3-Ph	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]piperazine	579	0.44 (50% EtOAc in hexane)	4.11	1	13, 14
242	2,4-Cl_2-Ph	4-Cl-Ph	H	1	3-MeO-Ph	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-methoxyphenyl)piperazine	541	0.31 (60% EtOAc in hexane)	3.62	1	13, 14
243	2,4-Cl_2-Ph	4-Cl-Ph	H	1	4-Cl-Ph	1-(4-chlorophenyl)-4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}piperazine	545	0.72 (EtOAc)	4.13	1	13, 14

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
244	2,4-Cl_2-Ph	4-Cl-Ph	H	1	4-CN-Ph	4-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile	536	0.3 (66% EtOAc in hexane)	3.61	1	13, 14
245	2,4-Cl_2-Ph	4-Cl-Ph	H	1	benzyl	1-benzyl-4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}piperazine	525	0.30 (EtOAc)	2.62	1	13, 14
246	2,4-Cl_2-Ph	4-Cl-Ph	H	1	cyclohexyl	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-cyclohexylpiperazine hydrochloride	519	0.07 (EtOAc)	2.61	1	13, 14
247	2,4-Cl_2-Ph	4-F-Ph	H	1	4-CF_3-Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine trifluoroacetate	563		3.73	2	10, 11, 12
248	2,4-Cl_2-Ph	4-MeO-Ph	H	1	2-HO-Ph	2-(4-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride	523		2.81	2	10, 11, 12

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
249	2,4-Cl_2-Ph	4-MeO-Ph	H	1	2-pyrazinyl	2-(4-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)pyrazine bis(trifluoroacetate)	509		2.59	2	10, 11, 12
250	2,4-Cl_2-Ph	4-MeO-Ph	H	1	3-CF_3-Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride	575		4.24	2	10, 11, 12
251	2,4-Cl_2-Ph	4-MeO-Ph	H	1	6-Me-2-pyridinyl	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-(6-methyl-2-pyridinyl)piperazine hydrochloride	522		2.19	2	10, 11, 12
252	2,4-Cl_2-Ph	4-MeO-Ph	H	1	4-CF_3-Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine	574		4.34	2	10, 11, 12
253	2,4-Cl_2-Ph	4-MeO-Ph	H	1	4-CF_3-Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride	574		4.34	2	10, 11, 12

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
254	2,4-Cl_2-Ph	4-MeO-Ph	H	1	4-HO-Ph	4-(4-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride	523		2.52	2	10, 11, 12
255	2,4-Cl_2-Ph	4-MeO-Ph	H	1	4-pyridinyl	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-pyridinyl)piperazine hydrochloride	508		2.56	2	10, 11, 12
256	2,4-Cl_2-Ph	4-MeO-Ph	H	1	4-pyridinyl-methyl	1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-pyridinylmethyl)piperazine dihydrochloride	522		2.04	2	10, 11, 12
257	2,5-Cl_2-Ph	4-Cl-Ph	H	1	4-CN-Ph	4-(4-{[1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile	536		3.69	1	8
258	2-CF_3-Ph	4-Cl-Ph	H	1	3-CF_3-Ph	1-({1-(4-chlorophenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl}carbonyl)-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride	579		4.25	2	10, 11, 12

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
259	2-Cl-Ph	4-Cl-Ph	H	1	2,4-F_2-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,4-difluorophenyl)piperazine hydrochloride	513		3.4	2	10, 11, 12
260	2-Cl-Ph	4-Cl-Ph	H	1	2-CN-Ph	2-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile hydrochloride	502		3.25	2	10, 11, 12
261	2-Cl-Ph	4-Cl-Ph	H	1	2-HO-Ph	2-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride	493		2.78	2	10, 11, 12
262	2-Cl-Ph	4-Cl-Ph	H	1	2-hydroxyethyl	2-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)ethanol hydrochloride	445		2.42	2	10, 11, 12
263	2-Cl-Ph	4-Cl-Ph	H	1	2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-pyridinyl)piperazine dihydrochloride	478		2.63	2	10, 11, 12

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
264	2-Cl-Ph	4-Cl-Ph	H	1	3-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride	545		4.24	2	10, 11, 12
265	2-Cl-Ph	4-Cl-Ph	H	1	3-Cl-Ph	1-(3-chlorophenyl)-4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}piperazine hydrochloride	511		4.13	2	10, 11, 12
266	2-Cl-Ph	4-Cl-Ph	*cyclo*-Pr	1	4-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride	585		3.7	2	13, 14
267	2-Cl-Ph	4-Cl-Ph	H	1	4-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride	545		4.21	2	10, 11, 12
268	2-Cl-Ph	4-Cl-Ph	*cyclo*-Pr	1	4-CN-Ph	4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile hydrochloride	542		3.29	2	13, 14

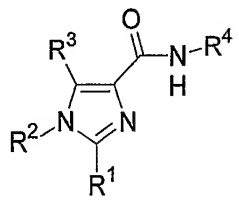
Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
269	2-Cl-Ph	4-Cl-Ph	H	1	4-CN-Ph	4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile	502		3.18	2	10, 11, 12
270	2-Cl-Ph	4-Cl-Ph	H	2	4-F-benzyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorobenzyl)-1,4-diazepane hydrochloride	523		2.68	2	10, 11, 12
271	2-Cl-Ph	4-Cl-Ph	H	1	4-F-benzyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorobenzyl)piperazine hydrochloride	509		2.67	2	10, 11, 12
272	2-Cl-Ph	4-Cl-Ph	H	1	4-HO-Ph	4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride	493		2.44	2	10, 11, 12
273	2-Cl-Ph	4-Cl-Ph	H	1	cyclohexyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-cyclohexylpiperazine hydrochloride	483		2.63	2	10, 11, 12

Table 10

Entry No.	R^1	R^2	R^3	n	R^{13}	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
274	2-Cl-Ph	4-Me-Ph	H	1	2-hydroxyethyl	2-(4-{[2-(2-chlorophenyl)-1-(4-methylphenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)ethanol hydrochloride	425		2.34	2	10, 11, 12
275	2-Cl-Ph	4-NO_2-Ph	Me	1	3-CF_3-Ph	1-{[2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]piperazine	570	0.35 (67% EtOAc in hexane)	3.64	1	8

Table 11



Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
276	2-Cl-Ph	4-Cl-Ph	H	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	520.3	0.35 (60% EtOAc in Hexane)	3.69	1	13,14
277	2-Cl-Ph	4-Cl-Ph	H	(1R,2R)-2-(benzyloxy)-cyclopentyl	N-[(1R,2R)-2-(benzyloxy)cyclopentyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	506.3	0.56 (50% EtOAc in Hexane)	3.51	1	13,14
278	2,4-Cl_2 Ph	4-Cl-Ph	H	(1R,2R)-2-(benzyloxy)-cyclohexyl	N-[(1R,2R)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide	554.4	0.46 (50% EtOAc in Hexane)	3.99	1	13,14
279	2,4-Cl_2 Ph	4-Cl-Ph	H	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide	554.4	0.46 (50% EtOAc in Hexane)	4.00	1	13,14

Table 11

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
280	2-Cl-Ph	4-Cl-Ph	H	(1R,2R)-2-(benzyloxy)-cyclohexyl	N-[(1R,2R)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxamide	520.3	0.33 (66% EtOAc in Hexane)	3.67	1	13,14
281	2,4-Cl_2 Ph	4-Cl-Ph	H	(1R,2R)-2-(benzyloxy)-cyclopentyl	N-[(1R,2R)-2-(benzyloxy)cyclopentyl]-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	540.0	0.41 (40% EtOAc in Hexane)	4.07	1	13,14
282	2,4-Cl_2 Ph	4-Cl-Ph	H	(1S,2S)-2-(benzyloxy)-cyclopentyl	N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	540.0	0.41 (40% EtOAc in Hexane)	4.07	1	13,14
283	2-Cl-Ph	4-Cl-Ph	H	(1S,2S)-2-(benzyloxy)-cyclopentyl	N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	506.1	0.32 (40% EtOAc in Hexane)	3.78	1	13,14
284	2-Cl-Ph	4-Cl-Ph	Et	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide	548.6	0.33 (33% EtOAc in Hexane)	3.81	1	13,14

Table 11

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
285	2-Cl-Ph	4-Cl-Ph	Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazole-4-carboxamide	562.2	0.20 (25% EtOAc in Hexane)	4.18	1	13,14
286	2-Cl-Ph	4-Cl-Ph	H	trans-2-(ethoxycarbonylmethoxy)-cyclohexyl	ethyl {[trans-2-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}amino)cyclohexyl]oxy}acetate	516.2	0.37 (67% EtOAc in Hexane)	3.37	1	13,14
287	2-Cl-Ph	4-Cl-Ph	H	trans-2-(2'-hydroxyethoxy)-cyclohexyl	2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-(2-hydroxyethoxy)cyclohexyl]-1H-imidazole-4-carboxamide	474.8	0.17 (EtOAc)	2.91	1	13,14
288	2-Cl-Ph	4-Br-Ph	Et	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide	592.9	0.29 (33% EtOAc in Hexane)	4.31	1	13,14
289	2-Cl-Ph	4-iPr-Ph	Et	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-isopropylphenyl)-2-(2-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide	556.3	0.79 (2:1 EtOAc/ Hexane)	4.09	1	13,14

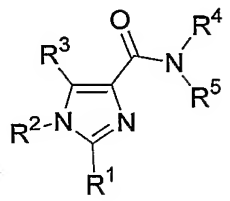
Table 11

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
290	2-Cl-Ph	4-Cl-Ph	Br	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	598		3.80	2	13,14
291	2-Cl-Ph	4-MeO-Ph	Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-methoxyphenyl)-5-propyl-1H-imidazole-4-carboxamide	558.3	0.60 (1:1 EtOAc/ Hexane)	3.86	1	13,14
292	2-Cl-Ph	4-F-Ph	Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-fluorophenyl)-5-propyl-1H-imidazole-4-carboxamide	546.3	0.19 (1:1 EtOAc/ Hexane)	3.90	1	13,14
293	2-Cl-Ph	3-Cl-Ph	Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(3-chlorophenyl)-5-propyl-1H-imidazole-4-carboxamide	562.3	0.73 (1:1 EtOAc/ Hexane)	4.07	1	13,14
294	2-Cl-Ph	2-Cl-4-F-Ph	H	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(2-chloro-4-fluorophenyl)-1H-imidazole-4-carboxamide	538.2	0.44 (1:1 EtOAc/ Hexane)	3.64	1	13,14

Table 11

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
295	2-Cl-Ph	2,4-F_2-Ph	H	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-1H-imidazole-4-carboxamide	522.2	0.29 (1:1 EtOAc/ Hexane)	3.56	1	13,14
296	2-Cl-Ph	4-CF_3O Ph	Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-trifluoromethoxyphenyl)-5-propyl-1H-imidazole-4-carboxamide	612.3	0.41 (1:1 EtOAc/ Hexane)	4.17	1	13,14
297	2-Cl-Ph	4-Cl-Ph	*i*-Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-isopropyl-1H-imidazole-4-carboxamide	562		3.98	2	13,14
298	2-Cl-Ph	4-Cl-Ph	*cyclo*-Pr	(1S,2S)-2-(benzyloxy)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazole-4-carboxamide	560.3		3.72	2	13,14

Table 12



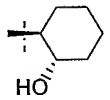
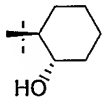
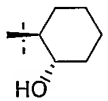
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
299	2-Cl-Ph	4-*i*-Pr-Ph	Et	H		2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-isopropylphenyl)-1H-imidazole-4-carboxamide	466	0.49 (2:1 EtOAc/ Hexane)	3.38	1	13,14
300	2-Cl-Ph	4-MeO-Ph	*n*-Pr	H		2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	468	0.66 (EtOAc)	3.09	1	13,14
301	2-Cl-Ph	4-F-Ph	*n*-Pr	H		2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide	456	0.35 (2:1 EtOAc/ Hexane)	3.16	1	13,14

Table 12

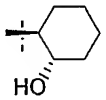
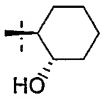
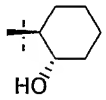
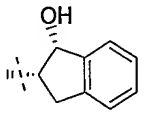
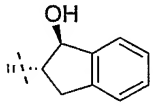
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
302	2-Cl-Ph	3-Cl-Ph	*n*-Pr	H		2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(3-chlorophenyl)-1H-imidazole-4-carboxamide	472	0.45 (2:1 EtOAc/ Hexane)	3.29	1	13,14
303	2-Cl-Ph	2-Cl-4-F-Ph	H	H		1-(2-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	448	0.5 (EtOAc)	2.90	1	13,14
304	2-Cl-Ph	2,4-F_2-Ph	H	H		2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	432	0.5 (EtOAc)	2.82	1	13,14
305	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[cis-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-1H-imidazole-4-carboxamide	464		3.16	1	13,14
306	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-1H-imidazole-4-carboxamide	464		3.15	1	13,14

Table 12

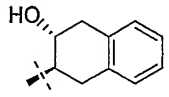
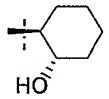
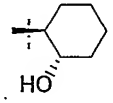
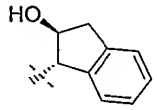
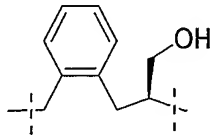
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
307	2-Cl-Ph	4-Cl-Ph	H	2,4-$(MeO)_2$-Ph-CH_2-		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,4-dimethoxybenzyl)-N-[trans-3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1H-imidazole-4-carboxamide	529	0.15 (1:1 EtOAc/ Hexane)	3.72	1	13,14
308	2-Cl-Ph	4-Cl-Ph	Br	H		5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	508		2.99	2	13,14
309	2-Cl-Ph	4-Cl-Ph	*i*-Pr	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-5-isopropyl-1H-imidazole-4-carboxamide	472		3.22	2	13,14
310	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide	464		3.05	2	10,11,12
311	2-Cl-Ph	4-Cl-Ph	H			((3S)-2-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1,2,3,4-tetrahydro-3-isoquinolinyl)methanol	478		3.00	2	10,11,12

Table 12

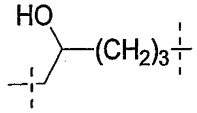
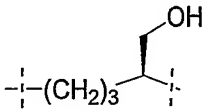
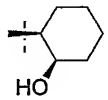
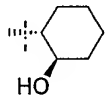
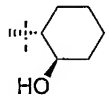
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
312	2-Cl-Ph	4-Cl-Ph	H			1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-3-piperidinol	416		2.56	2	10,11,12
313	2-Cl-Ph	4-Cl-Ph	H			((2S)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-2-pyrrolidinyl)methanol	416		2.59	2	10,11,12
314	2,4-Cl_2-Ph	4-MeO-Ph	H	H		2-(2,4-dichlorophenyl)-N-[cis-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	460		3.69	2	10,11,12
315	2,4-Cl_2-Ph	4-MeO-Ph	H	H		2-(2,4-dichlorophenyl)-N-[trans-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	460		3.40	2	10,11,12
316	2-Me-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-N-[trans-2-hydroxycyclohexyl]-2-(2-methylphenyl)-1H-imidazole-4-carboxamide	411		2.74	2	10,11,12

Table 12

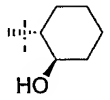
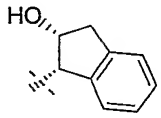
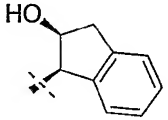
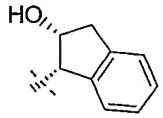
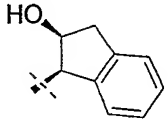
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
317	2,4-Cl_2-Ph	4-F-Ph	H	H		1-(4-fluorophenyl)-N-[trans-2-hydroxycyclohexyl]-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide	449		2.85	2	10,11,12
318	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide	498		3.29	2	10,11,12
319	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide	498		3.29	2	10,11,12
320	2-Cl-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide	464		3.11	2	10,11,12
321	2-Cl-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide	464		3.11	2	10,11,12

Table 12

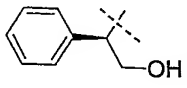
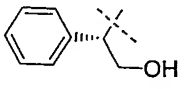
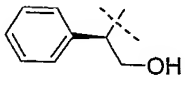
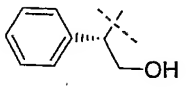
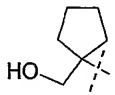
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
322	2,4-Cl_2-Ph	4-MeO-Ph	H	H		2-(2,4-dichlorophenyl)-N-[(1R)-2-hydroxy-1-phenylethyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	483		2.99	2	10,11,12
323	2,4-Cl_2-Ph	4-MeO-Ph	H	H		2-(2,4-dichlorophenyl)-N-[(1S)-2-hydroxy-1-phenylethyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide	483		2.96	2	10,11,12
324	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-N-[(1R)-2-hydroxy-1-phenylethyl]-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	452		2.88	2	10,11,12
325	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-N-[(1S)-2-hydroxy-1-phenylethyl]-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide	453		2.89	2	10,11,12
326	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(hydroxymethyl)cyclopentyl]-1H-imidazole-4-carboxamide	431		2.89	2	10,11,12

Table 12

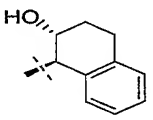
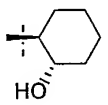
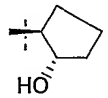
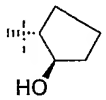
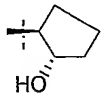
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
327	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl]-1H-imidazole-4-carboxamide	477		2.92	2	10,11,12
328	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[trans-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	464	0.14 (50% EtOAc in Hexane)	3.20	1	13,14
329	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide	416	0.43 (50% EtOAc in Hexane)	2.96	1	36
330	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide	450	0.45 (50% EtOAc in Hexane)	3.24	1	36
331	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide	450	0.45 (50% EtOAc in Hexane)	3.24	1	36

Table 12

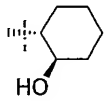
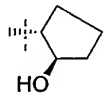
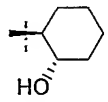
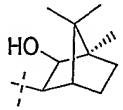
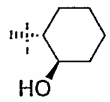
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
332	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	464	0.67 (EtOAc)	3.22	1	35
333	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide	416	0.4 (EtOAc)	2.83	1	36
334	2,4-Cl_2-Ph	4-Cl-Ph	H	H		1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	466	0.67 (EtOAc)	3.32	1	35
335	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1H-imidazole-4-carboxamide	484	0.22 (50% EtOAc in Hexane)	3.55	1	8
336	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	430	0.45 (5% MeOH in CH2Cl2)	2.95	1	13,14

Table 12

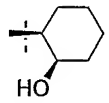
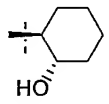
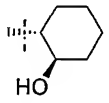
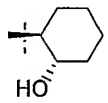
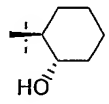
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
337	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[cis-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	430	0.31(66% EtOAc in Hexane)	2.94	1	13,14
338	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	430	0.30(66% EtOAc in Hexane)	3.02	1	35
339	2-Cl-Ph	4-Cl-Ph	H	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	430	0.30 (66% EtOAc in Hexane)	2.96	1	35
340	2-Cl-Ph	4-Cl-Ph	Et	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	458	0.37 (75% EtOAc in Hexane)	3.24	1	35
341	2-Cl-Ph	4-Cl-Ph	*n*-Pr	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	472	0.41 (75% EtOAc in Hexane)	3.38	1	35

Table 12

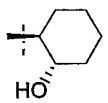
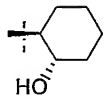
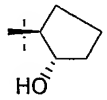
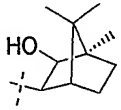
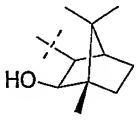
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
342	2-Cl-Ph	4-Br-Ph	Et	H		2-(2-chlorophenyl)-1-(4-bromophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	502	0.45 (EtOAc)	3.19	1	35
343	2-Cl-Ph	4-Cl-Ph	Me	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-methyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	444	0.29 (80% EtOAc in Hexane)	3.06	1	35
344	2-Cl-Ph	4-Cl-Ph	Et	H		2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide	444	0.30 (67% EtOAc in Hexane)	3.15	1	36
345	2-Cl-Ph	4-Br-Ph	Et	H		2-(2-chlorophenyl)-1-(4-bromophenyl)-N-[(1S,2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-5-ethyl-1H-imidazole-4-carboxamide	556	0.40 (50% EtOAc in Hexane)	3.97	1	8
346	2-Cl-Ph	4-Br-Ph	Et	H		2-(2-chlorophenyl)-1-(4-bromophenyl)-N-[(1R,2S,3R,4S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-5-ethyl-1H-imidazole-4-carboxamide	556	0.40 (50% EtOAc in Hexane)	4.00	1	8

Table 12

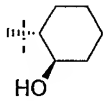
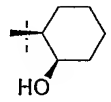
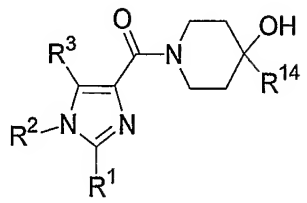
Entry No.	R^1	R^2	R^3	R^4	R^5	IUPAC name	MS m/z [MH+]	TLC (solvent)	HPLC ret. time (min)	HPLC method	Synthesis Method of Ex. No.
347	2-Cl-Ph	4-Br-Ph	Et	H		1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	502	0.45 (EtOAc)	3.31	1	35
348	2-Cl-Ph	4-Br-Ph	Et	H		1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[cis-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	502	0.26 (50% EtOAc in hexane)	502.3	1	23

Table 13



Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
349	2-Cl-Ph	4-Cl-Ph	H	1,1-dioxido-1-benzothien-2-yl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(1,1-dioxido-1-benzothien-2-yl)-4-piperidinol	580	0.29 (EtOAc)	3.10	1	18
350	2-Cl-Ph	4-Cl-Ph	H	1,3-thiazol-2-yl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(1,3-thiazol-2-yl)-4-piperidinol	499	0.10 (1:2 Hexane/ EtOAc)	2.83	1	18
351	2-Cl-Ph	4-Cl-Ph	H	1-benzofuran-2-yl	4-(1-benzofuran-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-piperidinol	532	0.45 (EtOAc)	3.44	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
352	2-Cl-Ph	4-Cl-Ph	Et	1-benzofuran-2-yl	4-(1-benzofuran-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-piperidinol	560	0.39 (EtOAc)	3.43	1	18
353	2-Cl-Ph	4-Cl-Ph	nPr	1-benzofuran-2-yl	4-(1-benzofuran-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-piperidinol	574	0.40 (EtOAc)	3.55	1	18
354	2-Cl-Ph	4-Cl-Ph	H	1-benzothien-2-yl	4-(1-benzothien-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-piperidinol	548	0.50 (EtOAc)	3.45	1	18
355	2-Cl-Ph	4-Cl-Ph	nPr	1-benzothien-2-yl	4-(1-benzothien-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-piperidinol	590	0.45 (EtOAc)	3.66	1	18
356	2-Cl-Ph	4-Cl-Ph	Et	1-benzothien-2-yl	4-(1-benzothien-2-yl)-1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-piperidinol	576	0.44 (EtOAc)	3.54	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
357	2-Cl-Ph	4-Cl-Ph	H	2,3-dihydro-1,4-benzodioxin-6-yl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-piperidinol	550	0.20 (1:2 Hexane/ EtOAc)	3.02	1	18
358	2-Cl-Ph	4-Cl-Ph	H	2,6-dimethyl-3-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,6-dimethyl-3-pyridinyl)-4-piperidinol	521	0.04 (EtOAc)	2.24	1	18
359	2-Cl-Ph	4-Cl-Ph	H	2,4-$(MeO)_2$-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,4-dimethoxyphenyl)-4-piperidinol	552	0.16 (1:2 Hexane/ EtOAc)	3.20	1	18
360	2-Cl-Ph	4-Cl-Ph	H	2,5-F_2-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,5-difluorophenyl)-4-piperidinol	528	0.24 (1:2 Hexane/ EtOAc)	3.28	1	18
361	2-Cl-Ph	4-Cl-Ph	H	2,5-$(MeO)_2$-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2,5-dimethoxyphenyl)-4-piperidinol	552	0.23 (1:2 Hexane/ EtOAc)	3.15	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
362	2-Cl-Ph	4-Cl-Ph	H	2-CF_3O-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[2-(trifluoromethoxy)phenyl]-4-piperidinol	576	0.22 (1:2 Hexane/ EtOAc)	3.45	1	18
363	2-Cl-Ph	4-Cl-Ph	H	2-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[2-(trifluoromethyl)phenyl]-4-piperidinol	560	0.24 (1:2 Hexane/ EtOAc)	3.41	1	18
364	2-Cl-Ph	4-Cl-Ph	H	2-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-chlorophenyl)-4-piperidinol	526	0.13 (1:2 Hexane/ EtOAc)	3.34	1	18
365	2-Cl-Ph	4-Cl-Ph	H	2-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-fluorophenyl)-4-piperidinol	510	0.13 (1:2 Hexane/ EtOAc)	3.24	1	18
366	2-Cl-Ph	4-Cl-Ph	H	2-furyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-furyl)-4-piperidinol	482	0.22 (1:2 Hexane/ EtOAc)	2.98	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
367	2-Cl-Ph	4-Cl-Ph	Et	2-furyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(2-furyl)-4-piperidinol	510	0.29 (1:2 Hexane/ EtOAc)	3.04	1	18
368	2-Cl-Ph	4-Cl-Ph	H	2-MeO-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-methoxylphenyl)-4-piperidinol	522	0.22 (1:2 Hexane/ EtOAc)	3.23	1	18
369	2-Cl-Ph	4-Cl-Ph	H	2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-pyridinyl)-4-piperidinol	493	0.05 (1:2 Hexane/ EtOAc)	2.26	1	18
370	2-Cl-Ph	4-Cl-Ph	H	2-thienyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(2-thienyl)-4-piperidinol	498	0.22 (1:2 Hexane/ EtOAc)	3.11	1	18
371	2-Cl-Ph	4-Cl-Ph	nPr	2-thienyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(2-thienyl)-4-piperidinol	540	0.41 (EtOAc)	3.33	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
372	2-Cl-Ph	4-Cl-Ph	Et	2-thienyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(2-thienyl)-4-piperidinol	526	0.42 (EtOAc)	3.20	1	18
373	2-Cl-Ph	4-Cl-Ph	Et	3-CF_3-4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol	622	0.47 (EtOAc)	3.73	1	18
374	2-Cl-Ph	4-Cl-Ph	nPr	3-CF_3-4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol	636	0.42 (EtOAc)	3.82	1	18
375	2-Cl-Ph	4-Cl-Ph	H	3-CF_3O-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol	576	0.38 (1:2 Hexane/ EtOAc)	3.37	1	18
376	2-Cl-Ph	4-Cl-Ph	Et	3-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]-4-piperidinol	588	0.46 (EtOAc)	3.55	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
377	2-Cl-Ph	4-Cl-Ph	nPr	3-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]-4-piperidinol	602	0.43 (EtOAc)	3.65	1	18
378	2-Cl-Ph	4-Cl-Ph	H	3-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-chlorophenyl)-4-piperidinol	526	0.18 (1:2 Hexane/ EtOAc)	3.39	1	18
379	2-Cl-Ph	4-Cl-Ph	Et	3-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(3-chlorophenyl)-4-piperidinol	554	0.42 (EtOAc)	3.44	1	18
380	2-Cl-Ph	4-Cl-Ph	nPr	3-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(3-chlorophenyl)-4-piperidinol	568	0.41 (EtOAc)	3.58	1	18
381	2-Cl-Ph	4-Cl-Ph	H	3-F-4-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-fluoro-4-(trifluoromethyl)phenyl]-4-piperidinol	578	0.22 (1:2 Hexane/ EtOAc)	3.53	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
382	2-Cl-Ph	4-Cl-Ph	H	3-F-4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-fluoro-4-chlorophenyl)-4-piperidinol	544	0.25 (1:2 Hexane/ EtOAc)	3.36	1	18
383	2-Cl-Ph	4-Cl-Ph	H	3-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-fluorophenyl)-4-piperidinol	510	0.24 (1:2 Hexane/ EtOAc)	3.19	1	18
384	2-Cl-Ph	4-Cl-Ph	Et	3-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(3-fluorophenyl)-4-piperidinol	538	0.43 (EtOAc)	3.30	1	18
385	2-Cl-Ph	4-Cl-Ph	nPr	3-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(3-fluorophenyl)-4-piperidinol	552	0.43 (EtOAc)	3.41	1	18
386	2-Cl-Ph	4-Cl-Ph	H	6-methyl-2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(6-methyl-2-pyridinyl)-4-piperidinol	507	0.32 (EtOAc)	2.29	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
387	2-Cl-Ph	4-Cl-Ph	Et	6-methyl-2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(6-methyl-2-pyridinyl)-4-piperidinol	535	0.27 (1:2 Hexane/ EtOAc)	2.75	1	18
388	2-Cl-Ph	4-Cl-Ph	H	3-Me-4-MeO-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-methoxy-3-methylphenyl)-4-piperidinol	537	0.20 (1:2 Hexane/ EtOAc)	3.25	1	18
389	2-Cl-Ph	4-Cl-Ph	H	3-MeO-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-methoxyphenyl)-4-piperidinol	522	0.24 (1:2 Hexane/ EtOAc)	3.12	1	18
390	2-Cl-Ph	4-Cl-Ph	H	3-thienyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-thienyl)-4-piperidinol	498	0.22 (1:2 Hexane/ EtOAc)	3.10	1	18
391	2-Cl-Ph	4-Cl-Ph	H	4,6-dimethyl-2-pyrimidinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4,6-dimethyl-2-pyrimidinyl)-4-piperidinol	522	0.09 (EtOAc)	2.55	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
392	2-Cl-Ph	4-Cl-Ph	H	4-CF_3O-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol	576	0.18 (1:2 Hexane/ EtOAc)	3.48	1	18
393	2-Cl-Ph	4-Cl-Ph	Et	4-CF_3O-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol	604	0.39 (EtOAc)	3.58	1	18
394	2-Cl-Ph	4-Cl-Ph	nPr	4-CF_3O-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol	618	0.40 (EtOAc)	3.70	1	18
395	2-Cl-Ph	4-Cl-Ph	Et	4-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethylphenyl)-4-piperidinol	588	0.42 (EtOAc)	3.55	1	18
396	2-Cl-Ph	4-Cl-Ph	nPr	4-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethylphenyl)-4-piperidinol	602	0.40 (EtOAc)	3.66	1	18

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
397	2-Cl-Ph	4-Cl-Ph	Et	4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(4-chlorophenyl)-4-piperidinol	554	0.42 (EtOAc)	3.48	1	17
398	2-Cl-Ph	4-Cl-Ph	nPr	4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(4-chlorophenyl)-4-piperidinol	568	0.38 (EtOAc)	3.57	1	17
399	2-Cl-Ph	4-Cl-Ph	H	4-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol	510	0.25 (1:2 Hexane/ EtOAc)	3.18	1	17
400	2-Cl-Ph	4-Cl-Ph	Et	4-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol	538	0.36 (EtOAc)	3.29	1	17
401	2-Cl-Ph	4-Cl-Ph	nPr	4-F-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol	552	0.36 (EtOAc)	3.41	1	17

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
402	2-Cl-Ph	4-Cl-Ph	H	5-methyl-2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(5-methyl-2-pyridinyl)-4-piperidinol	507	0.15 (1:2 Hexane/ EtOAc)	2.31	1	18
403	2-Cl-Ph	4-Cl-Ph	H	4-MeO-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-methoxyphenyl)-4-piperidinol	522	0.21 (1:2 Hexane/ EtOAc)	3.10	1	17
404	2-Cl-Ph	4-Cl-Ph	H	4-MeS-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(methylsulfanyl)phenyl]-4-piperidinol	538	0.18 (1:2 Hexane/ EtOAc)	3.29	1	18
405	2-Cl-Ph	4-Cl-Ph	H	4-methyl-2-pyridinyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-methyl-2-pyridinyl)-4-piperidinol	521	0.18 (EtOAc)	2.24	1	18
406	2-Cl-Ph	4-Cl-Ph	H	Et	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-ethyl-4-piperidinol	444	0.15 (1:2 Hexane/ EtOAc)	2.86	1	17

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
407	2-Cl-Ph	4-Cl-Ph	H	iso-butyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-isobutyl-4-piperidinol	472	0.10 (1:2 Hexane/ EtOAc)	3.24	1	17
408	2-Cl-Ph	4-Cl-Ph	H	Me	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-methyl-4-piperidinol	431	0.08 (1:2 Hexane/ EtOAc)	2.69	1	17
409	2-Cl-Ph	4-Cl-Ph	H	n-butyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-butyl-4-piperidinol	472	0.11 (1:2 Hexane/ EtOAc)	3.84	1	18
410	2-Cl-Ph	4-Cl-Ph	H	n-pentyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-pentyl-4-piperidinol	486	0.30 (EtOAc)	3.45	1	17
411	2-Cl-Ph	4-Cl-Ph	H	Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol	474		3.03	2	10, 11, 12

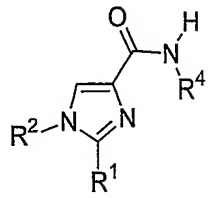
Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
412	2,4-Cl_2-Ph	4-MeO-Ph	H	Ph	1-{[2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol	522		3.55	2	10, 11, 12
413	2,4-Cl_2-Ph	4-Cl-Ph	H	Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol	526		3.33	2	10, 11, 12
414	2-Me-Ph	4-Cl-Ph	H	Ph	1-{[2-(2-methylphenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol	472		2.90	2	10, 11, 12
415	2,4-Cl_2-Ph	4-F-Ph	H	Ph	1-{[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol	509		3.03	2	10, 11, 12
416	2-Cl-Ph	4-Cl-Ph	H	4-Br-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-bromophenyl)-4-piperidinol	570		3.14	2	10, 11, 12

Table 13

Entry No.	R^1	R^2	R^3	R^{14}	IUPAC name	MS m/z (MH+1)	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
417	2-Cl-Ph	4-Cl-Ph	H	benzyl	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-benzyl-4-piperidinol	506		2.98	2	10, 11, 12
418	2-Cl-Ph	4-Cl-Ph	H	3-CF_3-4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol	594		3.38	2	10, 11, 12
419	2-Cl-Ph	4-Cl-Ph	H	4-Cl-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-chlorophenyl)-4-piperidinol	526		3.11	2	10, 11, 12
420	2-Cl-Ph	4-Cl-Ph	H	3-CF_3-Ph	1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluromethyl)phenyl]-4-piperidinol	560		3.17	2	10, 11, 12

Table 14



Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
421	2-Cl-Ph	3-pyridinyl	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(3-pyridinyl)-1H-imidazole-4-carboxamide	381.2	0.23 (4% MeOH in CH_2Cl_2)	2.71	1	8
422	2-Cl-3-pyridinyl	4-F-Ph	1-piperidinyl	2-(2-chloro-3-pyridinyl)-1-(4-fluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	400.3	0.19 (EtOAc)	2.32	1	10, 11, 12
423	4-CF_3-3-pyridinyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-N-(1-piperidinyl)-2-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carboxamide	450.3	0.45 (10% MeOH in EtOAc)	2.58	1	8
424	3-Me-2-pyridinyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(3-methyl-2-pyridinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	396.3	0.25 (EtOAc)	2.27	1	8

Table 14

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
425	3-Me-4-pyridinyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(3-methyl-4-pyridinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	396.3	0.30 (2% MeOH in EtOAc)	2.10	1	13, 14
426	4-CF_3-3-pyridinyl	4-Cl-Ph	2-CF_3-anilino	1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-2-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carbohydrazide hydrochloride	525		3.65	1	10, 11, 12
427	3-Me-2-thienyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(3-methyl-2-thienyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	401.2	0.22 (67% EtOAc in hexane)	2.8	1	6
428	2-furyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(2-furyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	371.2	0.27 (80% EtOAc in hexane)	2.57	1	6
429	2-Cl-Ph	5-t-Bu-3-isoxazolyl	1-piperidinyl	1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	428.2	0.12 (1:1 EtOAc/ hexane)	3.06	1	13, 14

Table 14

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
430	2-Cl-Ph	5-t-Bu-3-isoxazolyl	cyclohexyl	1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-cyclohexyl-1H-imidazole-4-carboxamide	427.2	0.39 (1:1 EtOAc/ hexane)	3.68	1	13, 14
431	2-Cl-Ph	5-t-Bu-3-isoxazolyl	2-(S)-benzyloxy-1-(S)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxamide	533.1	0.34 (1:1 EtOAc/ hexane)	3.89	1	13, 14
432	2-Cl-Ph	3-quinolinyl	1-piperidinyl	2-(2-chlorophenyl)-N-(1-piperidinyl)-1-(3-quinolinyl)-1H-imidazole-4-carboxamide	432.2	0.11 (EtOAc)	2.61	1	13, 14
433	2-Cl-Ph	3-quinolinyl	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(3-quinolinyl)-1H-imidazole-4-carboxamide	431.2	0.44 (EtOAc)	3.23	1	13, 14
434	2-Cl-Ph	3-quinolinyl	2-(S)-benzyloxy-1-(S)-cyclohexyl	N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(3-quinolinyl)-1H-imidazole-4-carboxamide	537.1	0.46 (EtOAc)	3.51	1	13, 14

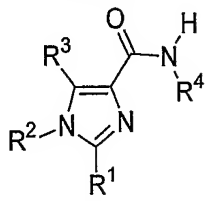
Table 14

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
435	2-Cl-Ph	5-t-Bu-3-isoxazolyl	2-(S)-hydroxy-1-(S)-cyclohexyl	1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide	443.2	0.43 (EtOAc)	3.07	1	35
436	2-Cl-Ph	3-quinolinyl	2-(S)-hydroxy-1-(S)-cyclohexyl	2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(3-quinolinyl)-1H-imidazole-4-carboxamide	447.2	0.19 (EtOAc)	2.65	1	35
437	2-Me-4-thiazolyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(2-methyl-1,3-thiazol-4-yl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	402.2	0.21 (EtOAc)	2.41	1	6
438	1-naphthyl	4-Cl-Ph	1-piperidinyl	1-(4-chlorophenyl)-2-(1-naphthyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	431.2	0.42 (EtOAc)	3.06	1	6
439	2-Cl-Ph	1,3-thiazol-2-yl	1-piperidinyl	2-(2-chlorophenyl)-N-(1-piperidinyl)-1-(1,3-thiazol-2-yl)-1H-imidazole-4-carboxamide	388.1	0.27 (EtOAc)	2.46	1	13, 14

Table 14

Entry No.	R^1	R^2	R^4	IUPAC name	MS m/z [MH+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
440	2-Cl-Ph	1,3-thiazol-2-yl	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(1,3-thiazol-2-yl)-1H-imidazole-4-carboxamide	387.1	0.52 (EtOAc)	3.15	1	13, 14

Table 15



Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
441	2-Cl-Ph	4-Cl-benzyl	Me	cyclohexyl	1-(4-chlorobenzyl)-2-(2-chlorophenyl)-N-cyclohexyl-5-methyl-1H-imidazole-4-carboxamide	442.2		2.65	1	8
442	2-Cl-Ph	1-piperidinyl	H	1-piperidinyl	2-(2-chlorophenyl)-N,1-di(1-piperidinyl)-1H-imidazole-4-carboxamide	388.3	0.10 (1:1 EtOAc/ hexane)	2.76	1	10, 11, 12
443	2-Cl-Ph	1-piperidinyl	H	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(1-piperidinyl)-1H-imidazole-4-carboxamide	387.3	0.38 (1:1 EtOAc/ hexane)	3.44	1	10, 11, 12
444	2-Cl-Ph	4-morpholinyl	H	1-piperidinyl	2-(2-chlorophenyl)-1-(4-morpholinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	390.4	0.13 (EtOAc)	2.21	1	10, 11, 12

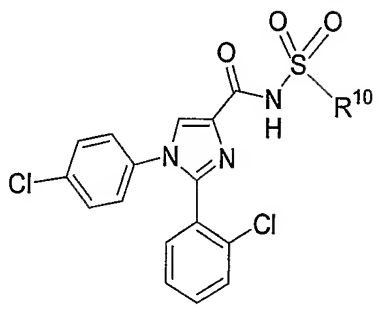
Table 15

Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
445	2-Cl-Ph	4-morpholinyl	H	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(4-morpholinyl)-1H-imidazole-4-carboxamide	389.3	0.13 (1:1 EtOAc/ hexane)	2.87	1	10, 11, 12
446	2-Cl-Ph	cyclohexyl	H	1-piperidinyl	2-(2-chlorophenyl)-1-cyclohexyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	387.4	0.18 (EtOAc)	2.60	1	10, 11, 12
447	2-Cl-Ph	cyclohexyl	H	cyclohexyl	2-(2-chlorophenyl)-N,1-dicyclohexyl-1H-imidazole-4-carboxamide	386.4	0.30 (1:1 EtOAc/ hexane)	3.23	1	10, 11, 12
448	2-Cl-Ph	4-Me-cyclohexyl	H	cyclohexyl	2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methylcyclohexyl)-1H-imidazole-4-carboxamide	400.4	0.38 (1:1 EtOAc/ hexane)	3.43	1	10, 11, 12
449	2-Cl-Ph	4-Me-cyclohexyl	H	1-piperidinyl	2-(2-chlorophenyl)-1-(4-methylcyclohexyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	401.4	0.32 (EtOAc)	2.83	1	10, 11, 12

Table 15

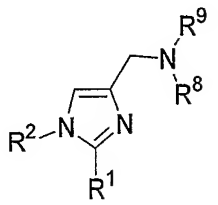
Entry No.	R^1	R^2	R^3	R^4	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min.)	HPLC method	Synthesis Method of Ex. No.
450	2-Me-1-propyl	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-isobutyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	361.2	0.28 (EtOAc)	2.43	1	6
451	2-Cl-Ph	4-F-benzyl	Et	1-piperidinyl	2-(2-chlorophenyl)-5-ethyl-1-(4-fluorobenzyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	441.2	0.21 (EtOAc)	2.75	1	13, 14
452	2-Cl-Ph	4-MeO-PhCO	Et	1-piperidinyl	2-(2-chlorophenyl)-5-ethyl-1-(4-methoxybenzoyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	467.2	0.24 (1:1 EtOAc/ hexane)	3.01	1	6
453	benzyl	4-Cl-Ph	H	1-piperidinyl	2-benzyl-1-(4-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide	395.2	0.26 (EtOAc)	2.75	1	6
454	n-hexyl	4-Cl-Ph	H	1-piperidinyl	1-(4-chlorophenyl)-2-hexyl-N-(1-piperidinyl)-1H-imidazole-4 carboxamide	389.2	0.30 (EtOAc)	3	1	6

Table 16



Entry No.	R^{10}	IUPAC name	MS m/z [MH+]	LC-MS RT (min)	HPLC method	Synthesis Method of Ex. No.
455	Me	N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}methanesulfonamide	410	2.70	2	16
456	4-CF_3-Ph	N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(trifluoromethyl)benzenesulfonamide	540	3.55	2	16
457	Ph	N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}benzenesulfonamide	472	3.14	2	16
458	4-MeO-Ph	N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-methoxybenzenesulfonamide	502	3.22	2	16

Table 17

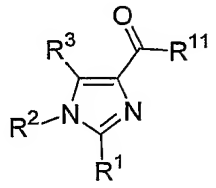


Entry No.	R^1	R^2	R^8	R^9	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
459	2-MeO-Ph	4-Cl-Ph	H	4-F-benzyl	N-{[1-(4-chlorophenyl)-2-(2-methoxyphenyl)-1H-imidazol-4-yl]methyl}-N-(4-fluorobenzyl)amine	422	0.3 (88% EtOAc in hexane)	2.48	1	33
460	2,4-Cl_2-Ph	4-F-Ph	Me	cyclohexyl	N-cyclohexyl-N-{[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]methyl}-N-methylamine	432	0.19 (10% MeOH in hexane)	2.65	1	34
461	2,4-Cl_2-Ph	4-Cl-Ph	H	4-F-benzyl	N-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}-N-(4-fluorobenzyl)amine	460	0.33 (10% MeOH in EtOAc)	2.88	1	33
462	2,4-Cl_2-Ph	4-Cl-Ph	H	4-CF_3-benzyl	N-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}-N-[4-(trifluoromethyl)benzyl]amine	510	0.33 (5% MeOH in EtOAc)	3.03	1	33

Table 17

Entry No.	R^1	R^2	R^8	R^9	IUPAC name	MS m/z [MH^+]	TLC Rf (solvent)	HPLC RT (min)	HPLC method	Synthesis Method of Ex. No.
463	2,4-Cl_2-Ph	4-Cl-Ph	H	trans-2-OH-cyclohexyl	trans-2-({[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}amino)cyclohexanol	451	0.3 (33% MeOH in EtOAc)	2.69	1	33
464	2,4-Cl_2-Ph	4-Cl-Ph	H	cyclohexyl	N-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}-N-cyclohexyamine	434	0.31 (25% MeOH in EtOAc)	2.83	1	33
465	2,4-Cl_2-Ph	4-Cl-Ph	H	4-(4-Me-Ph)-1-piperazinyl	1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}-4-(4-methylphenyl)piperazine bis(trifluoroacetate)	511		2.94	1	34
466	2-Cl-Ph	4-Cl-Ph	H	cyclohexyl	N-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]methyl}-N-cyclohexylamine	401	0.35 (50% EtOAc in MeOH)	2.32	1	33

Table 18



Entry No.	R^1	R^2	R^3	R^{11}	IUPAC Name	MS m/z (MH+)	TLC Rf (solvent)	HPLC RT (min) (LC-MS)	Synthesis Method of Ex. No.
467	2-Cl-Ph	4-Cl-Ph	Et	2-thienyl	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl](2-thienyl)methanone	427	0.13 (1:5 EtOAc/ Hexane)	3.93	31
468	2-Cl-Ph	4-Cl-Ph	H	n-propyl	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-butanone	359	0.49 (1:1 EtOAc/ Hexane)	3.30	29
469	2-Cl-Ph	4-Cl-Ph	H	1-methylpropyl	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-3-methyl-1-butanone	373	0.53 (1:1 EtOAc/ Hexane)	3.47	29
470	2-Cl-Ph	4-Cl-Ph	H	1-methylpropyl	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-2-methyl-1-butanone	373	0.56 (1:1 EtOAc/ Hexane)	3.47	29

Table 18

Entry No.	R^1	R^2	R^3	R^{11}	IUPAC Name	MS m/z (MH+)	TLC Rf (solvent)	HPLC RT (min) (LC-MS)	Synthesis Method of Ex. No.
471	2-Cl-Ph	4-Cl-Ph	H	n-pentyl	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-hexanone	387	0.56 (1:1 EtOAc/ Hexane)	3.71	29
472	2-Cl-Ph	4-Cl-Ph	H	cyclopentyl	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclopentyl)methanone	385	0.54 (1:1 EtOAc/ Hexane)	3.54	29
473	2-Cl-Ph	4-Cl-Ph	H	cyclohexyl	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclohexyl)methanone	399	0.56 (1:1 EtOAc/ Hexane)	3.71	29
474	2-Cl-Ph	4-Cl-Ph	H	4-F-Ph	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](4-fluorophenyl)methanone	411	0.58 (1:1 EtOAc/ Hexane)	3.57	29
475	2-Cl-Ph	4-Cl-Ph	H	4-Cl-Ph	(4-chlorophenyl)[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]methanone	427	0.37 (1:3 EtOAc/ Hexane)	3.83	29

Table 18

Entry No.	R^1	R^2	R^3	R^{11}	IUPAC Name	MS m/z (MH+)	TLC Rf (solvent)	HPLC RT (min) (LC-MS)	Synthesis Method of Ex. No.
476	2-Cl-Ph	4-Cl-Ph	H	2-MeO-Ph	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](3-methoxyphenyl)methanone	423	0.20 (1:3 EtOAc/ Hexane)	3.52	29
477	2-Cl-Ph	4-Cl-Ph	H	4-MeO-Ph	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](4-methoxyphenyl)methanone	423	0.18 (1:3 EtOAc/ Hexane)	3.51	29
478	2-Cl-Ph	4-Cl-Ph	H	Et	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-propanone	345	0.42 (1:1 EtOAc/ Hexane)	3.10	29
479	2-Cl-Ph	4-Cl-Ph	H	benzyl	1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-2-phenylethanone	407	0.51 (1:1 EtOAc/ Hexane)	3.54	29
480	2-Cl-Ph	4-Cl-Ph	H	Ph	[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](phenyl)methanone	393	0.5 (1:1 EtOAc/ Hexane)	3.48	29

Evaluation of Biological Activity

Evaluation of Compound's Efficacy on the Reduction of Food Intake in Lean Overnight Fasted Rats

Fasted-Refed Acute Feeding Assay

The purpose of this protocol is to determine the effect of a single dose of an unknown compound on food consumption of lean overnight fasted rats. The fasted-refed rat model is frequently used in the field of obesity to identify compounds with potential for anorectic effects. This animal model has been successfully used in the identification and characterization of the efficacy profile of compounds that are or have been used in the management of body weight in obese humans (*see, e.g.,* Balvet et al., Gen. Pharmacol. 13:293-297, 1982; Grignaschi et al., Br. J. Pharmacol. 127:1190-1194, 1999; McTavish and Heel, Drug 43:713-733, 1992; Rowland et al., Life Sci. 36:2295-2300, 1985).

A typical study includes 60-80 male rats (n=10/treatment group) with an average body weight of approximately 280 g. Rats are kept in standard animal rooms under controlled temperature and humidity and a 12/12 light dark cycle. Rats are single-housed in suspended cages with a mesh floor. Water and food are continuously available unless the animals are being fasted for the study.

The vehicle test: The rats are grouped based upon their performance on a vehicle test. The vehicle test is performed between 2 and 7 days before the efficacy test. The rats are fasted overnight during the dark phase (total of approx. 16-18 hrs). The animal is dosed with 0.5 mL deionized water. One hour after dosing, pre-weighed food jars are returned to the animal home cage. The rats are allowed one hour of feeding time. After 1 hour, the spillage is returned to the food jar and the amount of food consumed is determined. The rats are assigned to groups so that the mean and standard error of the mean of 1-hour food consumption are similar between groups.

The efficacy test: The rats are fasted overnight during the dark phase (total of approx. 16-18 hr). The animal is dosed with an assigned treatment (2 mg/ml). One hour after dosing, pre-weighed food jars are returned to the cage. Food intake is recorded 30, 60, 90, 180, and 240 minutes post-food return. At each time point, spillage is returned to the food jar and then the food jars are weighed. The amount of food consumed is determined for each time point. Difference between treatment group is determined using appropriate statistical analysis.

Compounds of the present invention were found to be active in this fasted-refed acute feeding assay. For example, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1S,2S)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., food consumption was reduced (relative to the food consumption observed for the

vehicle control group) by 34% to 62% when measured at time points from 30 to 240 minutes. Likewise, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*'-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide hydrochloride was dosed at 10 mg/kg p.o., food consumption was reduced (relative to the food consumption observed for the vehicle control group) by 31% to 53% when measured at time points from 30 to 240 minutes.

Evaluation of Compound's Efficacy on the Reduction of Body Weight and Food and Water Consumption in Obese Zucker fa/fa Rats

Chronic Feeding Assay

The purpose of this protocol is to determine the effect of chronic administration of an unknown compound on body weight and food and water consumption in obese Zucker fa/fa rats. Obese Zucker fa/fa rats are frequently used in the determination of compound efficacy in the reduction of body weight. This animal model has been successfully used in the identification and characterization of the efficacy profile of compounds that are or have been used in the management of body weight in obese humans (*see, e.g.,* Al-Barazanji et al., Obes Res. 8:317-323, 2000; Assimacopoulos-Jeannet et al., Am. J. Physiol. 260(2 Pt 2):R278-283, 1991; Dryden et al., Horm. Metab. Res. 31:363-366, 1999; Edwards and Stevens, Pharmacol. Biochem. Behav. 47:865-872, 1994; Grinker et al., Pharmacol. Biochem. Behav. 12:265-275, 1980).

A typical study includes 60-80 male Zucker fa/fa (n=10/treatment group) with an average body weight of approximately 550 g. Rats are kept in standard animal rooms under controlled temperature and humidity and a 12/12 light dark cycle. Water and food are continuously available. Rats are single-housed in large rat shoeboxes containing grid floor. Animals are adapted to the grid floors and sham-dosed with study vehicle for at least four days before the recording of two-days baseline measurement of body weight and 24-hr food and water consumption. Rats are assigned to one of 6-8 treatment groups based upon their body weight on baseline. The groups are set up so that the mean and standard error of the mean of body weight were similar.

Animals are orally gavaged (2 mL/kg) daily before the dark phase of the LD/cycle for a pre-determined number of days (typically 6-14 days) with their assigned dose/compound. At this time, body weight, food and water consumption are measured. On the final day, animals are euthanized by CO_2 inhalation, and the body weight is measured.

Compounds of this invention were found to be active in this chronic feeding assay. For example, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1S,2S)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide was dosed once a day at 10 mg/kg p.o., on day 6 of treatment the increase in body weight from baseline was approximately 2.4%, representing approximately 50% reduction in body weight gain as compared to the vehicle control group, where

an approximately 4.6% increase in body weight from baseline was observed. Likewise, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*'-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide hydrochloride was dosed once a day at 10 mg/kg p.o., on day 6 of treatment the increase in body weight from baseline was approximately 1.8%, representing approximately 60% reduction in body weight gain as compared to the vehicle control group, where an approximately 4.6% increase in body weight from baseline was observed.

Measurement of brain exposure

Male obese Zucker fa/fa rats were administered compounds, typically at 10 mg/kg p.o., and then brains were collected at 2 hours post-dosing for determination of brain concentration. Brains were weighed and homogenized with 4 mL 10 mM ammonium acetate buffer (pH 3), and the brain tissue homogenate samples were extracted via protein precipitation with acetonitrile. Samples were vortexed, centrifuged, and analyzed by liquid chromatography utilizing mass spectrometer selective detection (LC/MS/MS) using the heated nebulizer interface. Samples were quantitated using weighted ($1/x^2$) linear internal standard calibration curve. For example, when 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., a brain homogenate exposure level of approximately 200 nM was determined; when 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., a brain homogenate exposure level of approximately 200 nM was determined.

Demonstration of additional biological activities of the compounds of the present invention may be accomplished through *in vitro, ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of obesity-related disorders such as diabetes, Syndrome X, or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

Method for Measuring Blood Glucose Levels

db/db mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean blood glucose levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 14 days. At this point, the animals are bled again by eye or tail vein and blood glucose levels are determined. In each case, glucose levels are measured with a Glucometer Elite XL (Bayer Corporation, Elkhart, IN).

Method for Measuring Triglyceride Levels

hApoA1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 8 days. The animals are then bled again by eye or tail vein, and serum triglyceride levels are determined. In each case, triglyceride levels are measured using a Technicon Axon Autoanalyzer (Bayer Corporation, Tarrytown, NY).

Method for Measuring HDL-Cholesterol Levels

To determine plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once daily with vehicle or test compound for 7 days, and then bled again on day 8. Plasma is analyzed for HDL-cholesterol using the Synchron Clinical System (CX4) (Beckman Coulter, Fullerton, CA).

Method for Measuring Total Cholesterol, HDL-Cholesterol, Triglycerides, and Glucose Levels

In another *in vivo* assay, obese monkeys are bled, then orally dosed once daily with vehicle or test compound for 4 weeks, and then bled again. Serum is analyzed for total cholesterol, HDL-cholesterol, triglycerides, and glucose using the Synchron Clinical System (CX4) (Beckman Coulter, Fullerton, CA). Lipoprotein subclass analysis is performed by NMR spectroscopy as described by Oliver et al., (Proc. Natl. Acad. Sci. USA 98:5306-5311, 2001).

Method for Measuring an Effect on Cardiovascular Parameters

Cardiovascular parameters (e.g., heart rate and blood pressure) are also evaluated. SHR rats are orally dosed once daily with vehicle or test compound for 2 weeks. Blood pressure and heart rate are determined using a tail-cuff method as described by Grinsell et al., (Am. J. Hypertens. 13:370-375, 2000). In monkeys, blood pressure and heart rate are monitored as described by Shen et al., (J. Pharmacol. Exp. Therap. 278:1435-1443, 1996).

In addition, to demonstrate CNS activities of the compounds of the present invention, the following *in vivo* assays may be used.

Method for Testing Task Learning and Spatial Memory

The Morris Water Maze is routinely used to assess task learning and spatial memory (Jaspers et al., Neurosci. Lett. 117:149-153, 1990; Morris, J. Neurosci. Methods 11:47-60, 1984). In this assay, animals are placed in a water pool which is divided into quadrants. One platform is

hidden in one of the quadrants. The animal is placed in the water pool and is expected to locate the hidden platform within a predetermined time. During a number of training trials, the animal learns the location of the platform and escape from the pool. The animal receives multiple trials in this task. Total distance traveled, number of trials to locate platform, latency to find platform, and the swimming path is recorded for each animal. The animal's learning ability is measured by the length of time or number of trials required to find the hidden platform. Memory deficit or improvement is determined by the number of trials or the latency to find the platform at predetermined delay time after acquisition. Leaning and memory may be measured by the number of times that the animal crosses the quadrant where the platform was located during the acquisition phase.

Method for Testing Drug Dependence

Self-administration in animals is a predictor of a compound's abuse potential in humans. Modifications to this procedure may also be used to identify compounds that prevent or block the reinforcing properties of drugs that have abuse potential. A compound that extinguishes the self-administration of a drug may prevent that drug's abuse or its dependence. (Ranaldi et al., Psychopharmacol. 161:442-448, 2002; Campbell et al., Exp. Clin. Psychopharmacol. 8:312-25, 2000). In a self-administration test, animals are placed in the operant chambers containing both an active and inactive lever. Each response on the active lever produces an infusion of either the test compound or a drug known to be self-administered. Presses on the inactive lever have no effect, but are also recorded. Animals are then trained to self-administer compound/drug over a set period of time by having drug access during each daily session. Illumination of the chamber house light signals the beginning of the session and the availability of the compound/drug. When the session ends, the house light is turned off. Initially, a drug infusion occurs with every press of the active lever. Once lever-pressing behavior has been established, the number of presses to produce a drug infusion is increased. After stable compound/drug self-administration is obtained, the effect of a second compound on the drug-reinforced behavior may be evaluated. Administration of this second compound prior to the session can either potentiate, extinguish, or produce no change to the self-administrating behavior. Tests are conducted every two days, and the order of the administration of the test compound doses is controlled.

Pharmaceutical Compositions

Based on the above tests, or other well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the

compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered may generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

Of course, the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt thereof may be ascertained by those skilled in the art using conventional treatment tests.

The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound identified by the methods described herein, or a pharmaceutically acceptable salt or ester thereof. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds identified by the methods described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as

liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; an oil; a fatty acid; a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can

be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see,* e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine.

Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g., ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8,

caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride);

viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

The compounds identified by the methods described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-obesity, or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

The compounds identified by the methods described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may be prepared by any of the methods well known in the art (*see, e.g.,* Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000)

The following examples are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way.

Capsule Formulation

A capsule formula is prepared from:

Compound of this invention	40 mg
Starch	109 mg
Magnesium stearate	1 mg

The components are blended, passed through an appropriate mesh sieve, and filled into hard gelatin capsules.

Tablet Formulation

A tablet is prepared from:

Compound of this invention	25 mg
Cellulose, microcrystaline	200 mg
Colloidal silicon dioxide	10 mg
Stearic acid	5.0 mg

The ingredients are mixed and compressed to form tablets. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Sterile IV Solution

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

Intramuscular suspension

The following intramuscular suspension is prepared:

Compound of this invention	50 mg/ml
Sodium carboxymethylcellulose	5 mg/ml
TWEEN 80	4 mg/ml
Sodium chloride	9 mg/ml
Benzyl alcohol	9 mg/ml

The suspension is administered intramuscularly.

Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and

sorbitol to prepare a water miscible medicine mix.

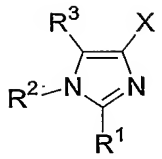
Immediate Release Tablets/Capsules

These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

The structures, materials, compositions, and methods described herein are intended to be representative examples of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

What is claimed:

1. A compound of Formula I,



(I)

wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, $(C_1–C_6)$alkyl sulfonyl, $(C_1–C_6)$alkyl sulfonyl-amino, $(C_1–C_6)$alkyl carbonyl-amino, $(C_1–C_6)$alkyl amino-carbonyl-amino, or phenyl,

$(C_2–C_6)$alkyl,

cyclohexyl optionally substituted with $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

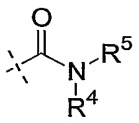
1-naphthyl or 2-naphthyl optionally substituted with halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is selected from

$(C_2–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted $(C_1–C_6)$alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy $(C_1–C_6)$alkyl, and optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

$–NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is $(C_1–C_9)$alkyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom; or

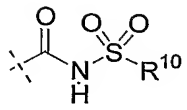
R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more $(C_1–C_6)$alkyl, $(C_1–$

C_6)alkoxy, hydroxy-substituted (C_1–C_3)alkyl, (C_1–C_3)alkoxy-substituted (C_1–C_3)alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or

X is 

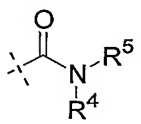
where R^{10} is (C_1–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl, or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, trifluoromethyl, benzyloxy, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

2. The compound of Claim 1, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is selected from

$(C_2–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted $(C_1–C_6)$alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy $(C_1–C_6)$alkyl, and optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

$–NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is $(C_1–C_9)$alkyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom; or

R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy-substituted $(C_1–C_3)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

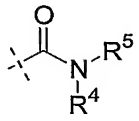
or

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted $(C_1–C_6)$alkyl, phenyl-substituted $(C_1–C_6)$alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

3. The compound of Claim 2, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

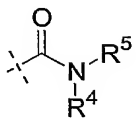
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted $(C_1–C_6)$alkyl, phenyl-substituted $(C_1–C_6)$alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

4. The compound of Claim 3, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

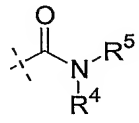
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperidin-1-yl or piperazin-1-yl group optionally substituted with one or more of fluorine, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted $(C_1–C_6)$alkyl, phenyl-substituted $(C_1–C_6)$alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

5. The compound of Claim 4, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

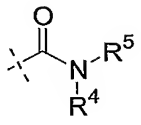
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, hydroxy-substituted $(C_1–C_6)$alkyl, phenyl-substituted $(C_1–C_6)$alkyl, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

6. The compound of Claim 5, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

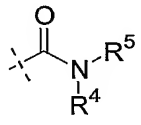
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

7. The compound of Claim 6, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, benzyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

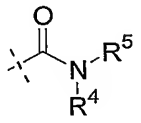
and pharmaceutical salts and esters thereof.

8. The compound of Claim 7, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, benzyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

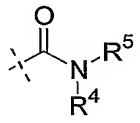
and pharmaceutical salts and esters thereof.

9. The compound of Claim 8, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

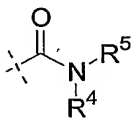
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, benzyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

10. The compound of Claim 4, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

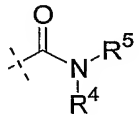
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperidin-1-yl group optionally substituted with one or more of fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

11. The compound of Claim 10, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

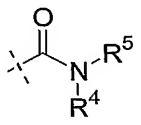
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperidin-1-yl group optionally substituted at the 4-position with one or more of fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

12. The compound of Claim 11, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

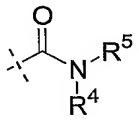
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a piperidin-1-yl group optionally substituted at the 4-position with one or more of fluorine, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, (C_1–C_6)alkyl-amino, bis[(C_1–C_3)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, cyano, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

13. The compound of Claim 12, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

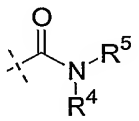
and pharmaceutical salts and esters thereof.

14. The compound of Claim 13, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

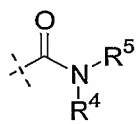
and pharmaceutical salts and esters thereof.

15. The compound of Claim 14, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C_1–C_6)alkyl, phenyl-substituted (C_1–C_6)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

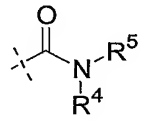
and pharmaceutical salts and esters thereof.

16. The compound of Claim 15, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

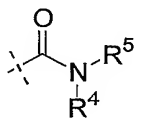
where

R^4 and R^5, taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group also substituted at the 4-position with (C_1–C_6)alkyl or with phenyl optionally substituted with one or more (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical esters thereof.

17. The compound of Claim 2, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is selected from

$(C_2–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted $(C_1–C_6)$alkyl, or fluorine,

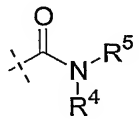
benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy $(C_1–C_6)$alkyl, and optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen;

and pharmaceutical salts and esters thereof.

18. The compound of Claim 17, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is selected from

$(C_2–C_9)$alkyl, optionally substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, $(C_1–C_6)$alkyl-amino, bis[$(C_1–C_3)$alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, hydroxy-substituted $(C_1–C_6)$alkyl, or fluorine,

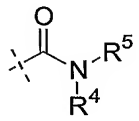
benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, and optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, or nitro,

piperidin-4-yl, optionally substituted on the nitrogen atom with $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, hydroxy, nitro, or halogen;

and pharmaceutical salts and esters thereof.

19. The compound of Claim 17, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

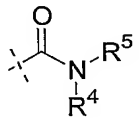
R^5 is selected from

cyclopentyl, cyclohexyl, benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which is substituted on one alkyl carbon with hydroxy, and optionally substituted on the phenyl ring, if present in R^5, with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

and pharmaceutical salts and esters thereof.

20. The compound of Claim 17, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

R^5 is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

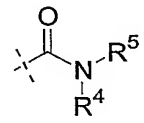
and pharmaceutical salts and esters thereof.

21. The compound of Claim 17, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl sulfonyl, (C_1–C_6)alkyl sulfonyl-amino, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen;

R^5 is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

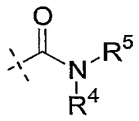
and pharmaceutical salts and esters thereof.

22. The compound of Claim 17, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen;

R^5 is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

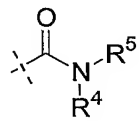
and pharmaceutical esters thereof.

23. The compound of Claim 17, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen;

R^5 is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

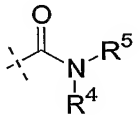
and pharmaceutical esters thereof.

24. The compound of Claim 17, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen;

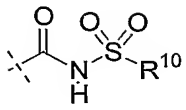
R^5 is selected from

(R,R)-2-hydroxycyclopentyl, (R,R)-2-hydroxycyclohexyl, (S,S)-2-hydroxycyclopentyl, or (S,S)-2-hydroxycyclohexyl;

and pharmaceutical esters thereof.

25. The compound of Claim 1, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

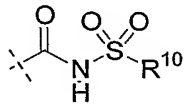
where R^{10} is $(C_1–C_9)$alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, trifluoromethyl, benzyloxy, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

26. The compound of Claim 25, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

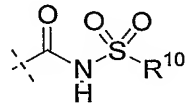
where R^{10} is $(C_1–C_9)$alkyl optionally substituted with one or more hydroxy or fluorine, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

27. The compound of Claim 26, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^{10} is $(C_1–C_9)$alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, or halogen;

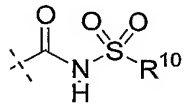
and pharmaceutical salts and esters thereof.

28. The compound of Claim 27, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl sulfonyl, (C_1–C_6)alkyl sulfonyl-amino, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^{10} is (C_1–C_9)alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, or halogen;

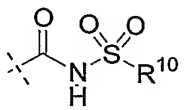
and pharmaceutical salts and esters thereof.

29. The compound of Claim 28, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

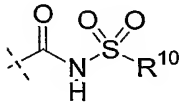
where R^{10} is $(C_1–C_9)$alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

30. The compound of Claim 29, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;
R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

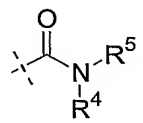
where R^{10} is $(C_1–C_9)$alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

31. The compound of Claim 1, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

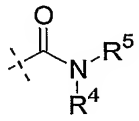
R^7 is $(C_1–C_9)$alkyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy-substituted $(C_1–C_3)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

and pharmaceutical salts and esters thereof.

32. The compound of Claim 31, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

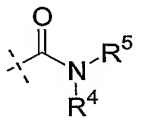
where

R^6 and R^7, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy-substituted $(C_1–C_3)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

and pharmaceutical salts and esters thereof.

33. The compound of Claim 32, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

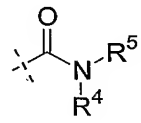
R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

and pharmaceutical salts thereof.

34. The compound of Claim 33, wherein

R^1 and R^2 are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl sulfonyl, (C_1–C_6)alkyl sulfonyl-amino, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen;

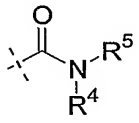
R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

and pharmaceutical salts thereof.

35. The compound of Claim 34, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro or bromo;

X is 

where R^4 is hydrogen;

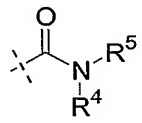
R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

and pharmaceutical salts thereof.

36. The compound of Claim 35, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen;

R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

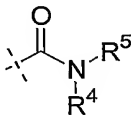
and pharmaceutical salts and esters thereof.

37. The compound of Claim 36, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

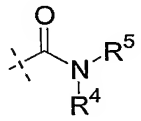
where R^4 is hydrogen;

R^5 is 1-piperidinyl, 1-pyrrolidinyl, or 1-azepanyl;

and pharmaceutical salts thereof.

38. The compound of Claim 31, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

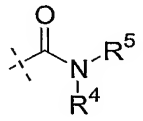
where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is $(C_1–C_9)$alkyl, or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy-substituted $(C_1–C_6)$alkyl, $(C_1–C_3)$alkoxy-substituted $(C_1–C_3)$alkyl, phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom;

and pharmaceutical salts and esters thereof.

39. The compound of Claim 38, wherein

R^1, R^2, and R^3 are defined as in Claim 1;

X is 

where R^4 is hydrogen;

R^5 is

$–NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or a halogen atom;

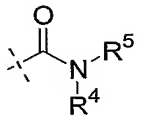
and pharmaceutical salts and esters thereof.

40. The compound of Claim 39, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, $(C_1–C_6)$alkyl sulfonyl, $(C_1–C_6)$alkyl sulfonyl-amino, $(C_1–C_6)$alkyl carbonyl-amino, $(C_1–C_6)$alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or a halogen atom;

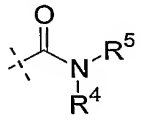
and pharmaceutical salts thereof.

41. The compound of Claim 40, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or a halogen atom;

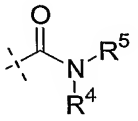
and pharmaceutical salts thereof.

42. The compound of Claim 41, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen;

R^5 is

$–NR^6R^7$

where R^6 is hydrogen or $(C_1–C_6)$alkyl;

R^7 is phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or a halogen atom;

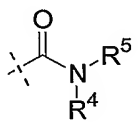
and pharmaceutical salts thereof.

43. The compound of Claim 42, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen;

R^5 is

$-NR^6R^7$

where R^6 is hydrogen or methyl;

R^7 is phenyl optionally substituted with one or more of trifluoromethyl, cyano, or a halogen atom;

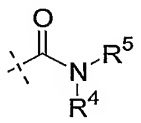
and pharmaceutical salts thereof.

44. The compound of Claim 1, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl sulfonyl, (C_1–C_6)alkyl sulfonyl-amino, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen or (C_1–C_6)alkyl;

X is 

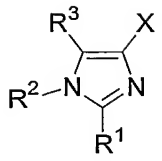
where R^4 is hydrogen;

R^5 is selected from

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C_1–C_6)alkyl, hydroxy-substituted (C_1–C_6)alkyl, (C_1–C_3)alkoxy-substituted (C_1–C_3)alkyl, benzyl, or phenyl optionally substituted with one or more of (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen;

and pharmaceutical salts and esters thereof.

45. A compound of Formula I,



(I)

wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, $(C_1–C_6)$alkyl carbonyl-amino, $(C_1–C_6)$alkyl amino-carbonyl-amino, or phenyl,

$(C_2–C_6)$alkyl,

cyclohexyl optionally substituted with $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

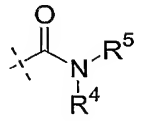
1- or 2-naphthyl optionally substituted with halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or phenyl, with the proviso that R^2 is not an unsubstituted 4-pyridyl or an unsubstituted 4-pyrimidinyl group;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

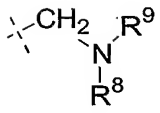
X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, hydroxy $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl,

or

X is 

where R^8 is a hydrogen or $(C_1–C_6)$alkyl;

R^9 is a $(C_1–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl group, each of which is optionally substituted with one or more of phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen, or

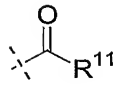
phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or halogen,

or

R^8 and R^9, together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of $(C_1–C_6)$alkyl, benzyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy,

halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or phenyl optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, or fluorine,

phenyl in which the phenyl ring is optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen,

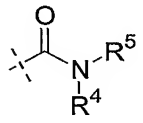
benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C_1–C_6)alkyl, and optionally substituted on the phenyl ring with halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

46. The compound of Claim 45, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^4 is hydrogen or (C_1–C_6)alkyl;

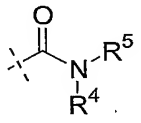
R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, hydroxy $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, optioanlly substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl;

and pharmaceutical salts and esters thereof.

47. The compound of Claim 46, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy, trifluoromethyl, or halogen, or

a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl;

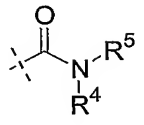
and pharmaceutical salts and esters thereof.

48. The compound of Claim 47, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, $(C_1–C_6)$alkyl carbonyl-amino, $(C_1–C_6)$alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy, trifluoromethyl, or halogen, or

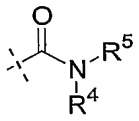
a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl;

and pharmaceutical salts and esters thereof.

49. The compound of Claim 48, wherein

R^1 and R^2 are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy, trifluoromethyl, or halogen, or

a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl;

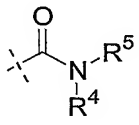
and pharmaceutical salts and esters thereof.

50. The compound of Claim 49, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^4 is hydrogen or $(C_1–C_6)$alkyl;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy, trifluoromethyl, or halogen, or

a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, or trifluoromethyl;

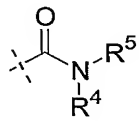
and pharmaceutical salts and esters thereof.

51. The compound of Claim 50, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

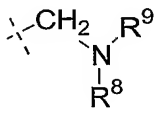
where R^4 is hydrogen;

R^5 is phenyl substituted with one or more $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, hydroxy, trifluoromethyl, or halogen;

and pharmaceutical salts and esters thereof.

52. The compound of Claim 45, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^8 is a hydrogen or $(C_1–C_6)$alkyl;

R^9 is a $(C_1–C_9)$alkyl or $(C_7–C_{11})$bicycloalkyl group, each of which is optionally substituted with one or more of phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, or halogen,

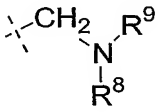
or

R^8 and R^9, together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of $(C_1–C_6)$alkyl, benzyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or phenyl optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, benzyloxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

53. The compound of Claim 52, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^8 is a hydrogen or $(C_1–C_6)$alkyl;

R^9 is a $(C_1–C_9)$alkyl, optionally substituted with one or more of hydroxy or fluorine, or

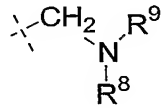
benzyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

54. The compound of Claim 53, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, $(C_1–C_6)$alkyl, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, nitro, $(C_1–C_6)$alkyl carbonyl-amino, $(C_1–C_6)$alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, $(C_1–C_6)$alkyl, benzyl, chloro, or bromo;

X is 

where R^8 is a hydrogen or $(C_1–C_6)$alkyl;

R^9 is a $(C_1–C_9)$alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of $(C_1–C_6)$alkyl, hydroxy, $(C_1–C_6)$alkoxy, trifluoromethyl, cyano, or halogen,

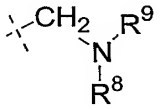
and pharmaceutical salts and esters thereof.

55. The compound of Claim 54, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^8 is a hydrogen or (C_1–C_6)alkyl;

R^9 is a (C_1–C_9)alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

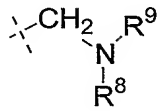
and pharmaceutical salts and esters thereof.

56. The compound of Claim 55, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^8 is a hydrogen or (C_1–C_6)alkyl;

R^9 is a (C_1–C_9)alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

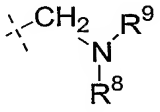
and pharmaceutical salts and esters thereof.

57. The compound of Claim 56, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^8 is a hydrogen or (C_1–C_6)alkyl;

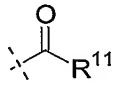
R^9 is cyclohexyl or 2-hydroxycyclohexyl, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

58. The compound of Claim 45, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, benzyloxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, or halogen,

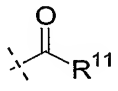
benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C_1–C_6)alkyl, and optionally substituted on the phenyl ring with halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

59. The compound of Claim 58, wherein

R^1, R^2, and R^3 are defined as in Claim 45;

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, (C_1–C_6)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

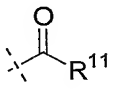
and pharmaceutical salts and esters thereof.

60. The compound of Claim 59, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, cyano, nitro, (C_1–C_6)alkyl carbonyl-amino, (C_1–C_6)alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, (C_1–C_6)alkoxy, or fluorine,

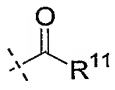
phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

61. The compound of Claim 60, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1–C_6)alkyl, benzyl, chloro, or bromo;

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, (C_1–C_6)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

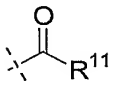
and pharmaceutical salts and esters thereof.

62. The compound of Claim 61, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^{11} is (C_2–C_9)alkyl optionally substituted with one or more phenyl, hydroxy, (C_1–C_6)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

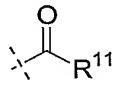
and pharmaceutical salts and esters thereof.

63. The compound of Claim 62, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1–C_6)alkyl, (C_1–C_6)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

X is 

where R^{11} is (C_2–C_9)alkyl,

phenyl, optionally substituted with one or more of (C_1–C_6)alkyl, hydroxy, (C_1–C_6)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

64. A compound selected from the group consisting of:

1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-chlorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluromethyl)phenyl]-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-fluorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl}-4-(3-chlorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(3-fluoro-4-chlorophenyl)-4-piperidinol;
1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide;
[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclohexyl)methanone;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;

N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide;

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;

1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;

1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide;

1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;

1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;

1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide;

1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(cis)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

4-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile; and
4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile.

65. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising an effective amount of a compound of claim 64, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more hypoglycemic agents.

69. The pharmaceutical composition of claim 68, wherein said hypoglycemic agent is selected from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α-glycosidase inhibitors, and β_3-adrenoreceptor agonists.

70. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more hypoglycemic agents.

71. The pharmaceutical composition of claim 70, wherein said hypoglycemic agent is selected from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α-glycosidase inhibitors, and β_3-adrenoreceptor agonists.

72. A pharmaceutical composition comprising an effective amount of a compound of claim 64, or a pharmaceutically acceptable salt or ester thereof, in combination with a

pharmaceutically acceptable carrier and one or more hypoglycemic agents.

73. The pharmaceutical composition of claim 72, wherein said hypoglycemic agent is selected from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α-glycosidase inhibitors, and β_3-adrenoreceptor agonists.

74. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

75. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

76. A pharmaceutical composition comprising an effective amount of a compound of claim 64, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

77. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

78. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

79. A pharmaceutical composition comprising an effective amount of a compound of claim

64, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

80. A composition comprising an effective amount of a compound of claim 1, or a salt or ester thereof, in combination with an inert carrier.

81. A composition comprising an effective amount of a compound of claim 45, or a salt or ester thereof, in combination with an inert carrier.

82. A composition comprising an effective amount of a compound of claim 64, or a salt or ester thereof, in combination with an inert carrier.

83. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

84. The method of claim 83, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.

85. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

86. The method of claim 85, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.

87. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 64.

88. The method of claim 87, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.

89. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

90. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

91. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

92. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

93. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

94. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

95. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more hypoglycemic agents.

96. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more hypoglycemic agents.

97. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 64 in combination with one or more hypoglycemic agents.

98. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more agents that modulate digestion and/or metabolism.

99. The method of claim 98, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

100. The method of claim 99, wherein said agents that modulate digestion and/or metabolism include β_3-adrenoreceptor agents.

101. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more agents that modulate digestion and/or metabolism.

102. The method of claim 101, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

103. The method of claim 102, wherein said agents that modulate digestion and/or metabolism include β_3-adrenoreceptor agents.

104. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64 in combination with one or more agents that modulate digestion and/or metabolism.

105. The method of claim 104, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

106. The method of claim 105, wherein said agents that modulate digestion and/or metabolism

include β_3-adrenoreceptor agents.

107. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

108. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

109. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.

110. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

111. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

112. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

113. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

114. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 45.

115. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

116. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

117. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

118. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30545

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/90 C07D401/04 C07D405/04 C07D409/04 C07D413/04
A61K31/415 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 40207 A (SIERRA MICHAEL LAWRENCE ;GLAXO GROUP LTD (GB)) 7 June 2001 (2001-06-07) claims; examples	1-118
Y	WO 00 69849 A (ORTHO MCNEIL PHARM INC) 23 November 2000 (2000-11-23) page 32 -page 42	1-118
P,Y	WO 02 064136 A (CHUGAI PHARMACEUTICAL CO LTD ;CHEN MI (US); CHENG JIE FEI (US); HU) 22 August 2002 (2002-08-22) claims; examples 22,23	1-118
Y	WO 98 27065 A (ONTOGEN CORP) 25 June 1998 (1998-06-25) page 73 -page 74; claims; examples	1-118

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2003	17/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Menegaki, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/30545

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 88-118 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International on patent family members

International Application No
PCT/US 02/30545

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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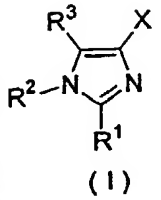
(54) Title: IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF OBESITY



(I)

(57) Abstract: This invention relates to substituted imidazole derivatives of formula I, which have been found to suppress appetite and induce weight loss. The invention also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders.

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